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SECURING THE PHARMACEUTICAL SUPPLY CHAIN

HEARING

OF THE

COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS

UNITED STATES SENATE

ONE HUNDRED TWELFTH CONGRESS

FIRST SESSION

ON

EXAMINING SECURING THE PHARMACEUTICAL SUPPLY CHAIN, FOCUSING ON HOW THE FOOD AND DRUG ADMINISTRATION FACES CHALLENGES OVERSEEING THE FOREIGN DRUG MANUFACTURING SUPPLY CHAIN

SEPTEMBER 14, 2011

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SECURING THE PHARMACEUTICAL SUPPLY CHAIN

WEDNESDAY, SEPTEMBER 14, 2011

U.S. SENATE,
COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS,
Washington, DC.

The committee met, pursuant to notice, at 10:02 a.m., in Room SD–430, Dirksen Senate Office Building, Hon. Tom Harkin, chairman of the committee, presiding.

Present: Senators Harkin, Mikulski, Franken, Bennet, Whitehouse, Blumenthal, Enzi, and Roberts.

OPENING STATEMENT OF SENATOR HARKIN

The CHAIRMAN. Good morning. The Senate Committee on Health, Education, Labor, and Pensions will come to order.

As part of our ongoing process to reauthorize the FDA user fee legislation in this Congress, we've convened this hearing to examine the safety and integrity of our pharmaceutical supply chain. Few issues are more important to the health and safety of Americans than the integrity of our drug supply.

In today's increasingly global economy, most of the key ingredients used in the drugs prescribed by American doctors and consumed by American families are produced overseas. According to a GAO study, about 80 percent of the active ingredients found in U.S. pharmaceutical products come from abroad, and about 40 percent of the finished drugs come from abroad.

This trend is projected to continue to increase with more and more of our medicine cabinets being stocked with products from countries like India and China who have less robust regulatory systems than our own. Our challenge is to embrace the promise of this increasingly global economy while still making sure we protect American patients.

The profound interests at stake are highlighted for us by tragic examples of American patients who have taken adulterated drug products, such as the 150 U.S. patients who died in 2007 after taking the contaminated Heparin. Weaknesses in our pharmaceutical supply chain not only affect the health of American patients but also the health of American businesses. By holding foreign actors to the same standards as those in the United States we guarantee a level playing field. U.S. companies that source and manufacture drugs in this country should not be placed at a competitive disadvantage by foreign firms that operate with less oversight and sell substandard ingredients into this country at reduced prices.

When FDA's authorities were first designed and enacted, our production methods were based here at home. FDA's primary authorities to ensure the quality of our drugs—which was strict oversight of domestic manufacturers coupled with the ability to interdict illegal drugs at the border—were well-suited to the manufacturing practices of that time in the late 1930s. But, again, that was nearly 100 years ago. We don't live in the same world as we did then, and our drug safety controls have failed to keep up with the changes in our economy and our society.

FDA and Customs have tried to increase their vigilance to keep pace with the increasingly global nature of our supply chain. But FDA does not have the authority and flexibility it needs to make sure that foreign facilities adhere to the same quality standards as U.S. facilities. Some domestic companies have tried to fill that gap by adopting robust quality control practices that include inspecting their overseas suppliers. Some have done it. Others have not. So the result is a supply chain rife with gaps.

Last year, this committee took an important bipartisan step to modernize our food safety system, giving FDA the tools necessary to hold foreign food importers and producers to the same safety standards as those in the United States. Now we have to bring our drug supply system also into the 21st Century.

This morning, we'll explore systemic concerns associated with the drugs and drug ingredients imported into the United States from abroad. We'll learn about the new challenges that both the FDA and the American pharmaceutical companies face in navigating the global economy. As we begin the critical discussion on how to modernize our drug supply system, we'll hear from several expert witnesses who approach this important issue through a variety of perspectives.

I thank all of you for being here and look forward to your testimonies. I look forward to continued bipartisan cooperation with my colleague, Ranking Member Enzi, who has worked closely with me on scheduling this hearing and who, himself, has devoted considerable energy to examining this issue.

And now I would recognize Senator Enzi.

STATEMENT OF SENATOR ENZI

Senator ENZI. Thank you, Mr. Chairman.

In 2007 and 2008, dozens of patients died after receiving Heparin, a widely-used blood thinner that had been contaminated during manufacture in China. The number of drug products made outside of the United States doubled from 2001 to 2008. This trend will accelerate, creating potential risks to patients from substandard and otherwise adulterated drugs.

Today's hearing will examine our increasingly global supply chain and assess how effective agencies like the FDA have been in protecting American consumers. The Government Accountability Office has found that the FDA does not police the drug supply chain effectively and recommended that the agency make several specific policy changes to address these problems. Unfortunately, FDA has failed to adequately respond to these recommendations.

Some of these GAO recommendations have been outstanding since the late 1990s. FDA has still not implemented them. In part

due to these failures and the corresponding risk to public health, GAO has placed FDA on its high-risk watch list of government programs. GAO has not called for sweeping legislation to solve these problems. Instead, GAO calls for FDA to administer its programs and manage its responsibilities more effectively.

Following the HELP Committee's July hearing with Commissioner Hamburg, I asked FDA a question for the record concerning the progress it has made on the GAO's recommendations. I still have not received a reply.

We all want to make sure FDA has the tools it needs to make sure drugs are safe and effective. To do that, we need to obtain the facts. It'll be hard for us to devise solutions if FDA is not more forthcoming about the facts and more responsive to Congress.

Having said that, I understand that legislation to improve supply chain integrity is a top priority for Chairman Harkin and Commissioner Hamburg. I look forward to working with them. And let me suggest four principles to guide our work together.

Our first principle should be that we are as specific as possible in identifying the problem we're trying to solve. One good example of a specific problem is, under current law, FDA must inspect domestic drug establishments every 2 years. But the law is silent about how often FDA must inspect foreign drug establishments. This means risky foreign establishments can avoid FDA inspections, and American companies bear more regulatory burden.

Heather Bresch, the CEO of Mylan, has championed a change in law to level the playing field. I agree. FDA should be able to target inspections globally based on risk.

Second principle—before making a new law, we should ask if FDA is using its existing authorities effectively. For instance, FDA promulgates current good manufacturing practices, or GMPs, to tell companies how to manufacture drugs. Despite all the obvious risks of globalization, FDA has not updated its GMPs on point.

The Active Pharmaceutical Ingredient Guide was last published in 1998, and the Quality Systems Approach Guidance was last published in 2006. FDA published a GMP Questions and Answers Guidance earlier this year, but it does not address the globalization challenges we're discussing today. We need to know why FDA hasn't updated its know-your-suppliers GMPs.

Third principle—we should develop solutions that actually solve the problem. Some ideas sound good in speeches, are politically dramatic, and make us feel like we're, "doing something." But they won't necessarily make a dent in the real-world problem.

For instance, some stakeholders advocate giving FDA mandatory recall authority for drugs. We can discuss that, but I'm skeptical it will make a real difference. FDA already has mandatory recall authority for medical devices and several other types of products. But according to GAO and the Institute of Medicine, FDA has only used its mandatory recall authority for devices three times.

Examining the data, GAO found the average time it took FDA to effectuate a Class I medical device recall—those posing the greatest risk to consumers—was 516 days. Also, these recalls were not always effective. There were situations where devices that should have been recalled were implanted in patients, causing sev-

eral deaths and serious injuries. And, remember, this is when the FDA already had mandatory recall authority.

Fourth principle—as we legislate, we should not over-reach. For example, some stakeholders advocate for a complete pedigree or track-and-trace system for the distribution of drugs. A 2008 Accenture study pegged the cost of a full track-and-trace system at up to $110,000 for an individual pharmacy.

Small, independent pharmacists in Wyoming are already under intense pressure from cuts in Medicare Part D and Medicaid reimbursement. They are small businesses and can't afford this additional cost. Moreover, most counterfeit and substandard drugs reach consumers through Internet sales, not retail pharmacies. Track-and-trace could impose tremendous costs on pharmacies but produce only a marginal effect.

Again, I look forward to working with Chairman Harkin on all these issues. I have been a strong supporter of giving FDA the tools it needs. For example, Senator Kennedy and I co-sponsored a drug safety bill in 2007. The New England Journal of Medicine said it was the most significant drug safety bill in a half century.

I also helped with the FDA new food safety and tobacco authorities. But right now, my concern is FDA over-regulating, not under-regulating.

In closing, I want to acknowledge that FDA's witness today, Deb Autor, only recently assumed her new position as deputy commissioner. She inherited many challenges.

Deputy Commissioner, you deserve credit for taking on a tough job, and I look forward to your testimony.

The CHAIRMAN. Thank you very much, Senator Enzi.

We have, basically, two panels. Our first panel will be Deborah Autor. Ms. Autor is the Deputy Commissioner for Global Regulatory Operations and Policy at the FDA. In this capacity, she leads the FDA in ensuring the integrity of our pharmaceutical supply chain and is responsible for imports, inspections, and enforcement policy for all FDA-regulated products. Ms. Autor also worked to secure our supply chain in her previous position as the Director of the Office of Compliance at FDA's Center for Drugs.

So welcome to the committee. Thank you for joining us today, Ms. Autor. Your statement will be made a part of the record in its entirety. If you could sum it up in 5 or 7 minutes, we'd certainly appreciate it so we can get into a discussion. So please proceed.

STATEMENT OF DEBORAH M. AUTOR, J.D., ESQ., DEPUTY COMMISSIONER FOR GLOBAL REGULATORY OPERATIONS AND POLICY, FDA, SILVER SPRING, MD

Ms. AUTOR. Thank you. Good morning, Chairman Harkin and members of the committee. I'm Deborah Autor, FDA's Deputy Commissioner for Global Regulatory Operations and Policy. Thank you for the opportunity to testify before you today about drug safety and globalization.

Globalization has fundamentally altered drug manufacturing and supply, greatly increasing the risks to American consumers. And it demands a major change in the way FDA fulfills its mission to promote and protect the health of the American people.

Based on almost 20 years of professional experience, I have witnessed the expanding gap between the globalization of pharmaceutical manufacturing and FDA's antiquated domestically focused statute. This gap presents an immediate and ever-growing risk to the safety of the American drug supply. It provides an opportunity for criminals to introduce dangerous, adulterated, counterfeit, and stolen product into the supply chain, at great risk to patients and at great cost to pharmaceutical companies.

The facts show that threats to our supply chain are real. Recent incidents of adulteration, counterfeiting, and cargo theft could pose serious threats to public health. The consequences throughout the world have been tragic.

In recent years, glycerin in fever medicine, cough syrup, and teething products was adulterated with a highly toxic solvent, diethylene glycol, resulting in the death of hundreds of adults and children in Haiti, Panama, and Nigeria. And members of this committee are well aware of the 2008 Heparin contamination crisis. Heparin is a blood thinner used in every hospital in this country. But a cheap Heparin imposter was substituted for the real drug, leading to tragic deaths and illnesses in the United States.

Similar to contaminated drugs, counterfeit drugs present real risks. A counterfeit drug could be made up of a substance that is toxic to patients or have little or no active ingredient, harming patients who take it, thinking that they are taking a life-saving or life-sustaining medication.

In 2003, over $20 million in counterfeit and illegally imported Lipitor, a popular cholesterol lowering drug, was dispensed to patients at pharmacies throughout the United States. Even more frightening, the criminals mixed illegal Lipitor with real Lipitor, presumably to avoid detection. Although the counterfeit reached all parts of the country, fortunately, we believe patient harm was minimal. Eventually, we will not be so lucky.

Just last year, a counterfeit version of the approved OTC weight loss drug, Alli, was sold over the Internet to U.S. consumers. Instead of the approved active ingredient, it contained high levels of a dangerous controlled substance, placing consumers at great jeopardy.

Cargo thefts of prescription drugs also pose a significant public health risk. In 2009 alone, at least 46 drug cargo thefts occurred valued at a total of $184 million, a great expense to pharmaceutical companies.

In March 2010, thieves broke into a warehouse and stole $75 million worth of prescription drug products, including chemotherapy drugs, anti-depressants, and blood thinners. These products have not yet been recovered, and we fear that they could be distributed to U.S. consumers in spite of public warnings.

In 2009, stolen insulin vials were reintroduced into the drug supply and caused adverse events in patients. The stolen insulin, which required refrigeration, lost its potency and did not provide the needed glucose control for diabetics.

These are just some examples that illustrate the enormous challenges that globalization presents to FDA, pharmaceutical manufacturers, and the American public.

The drug supply chain is a complex path that medical products travel from raw source materials to finished products for consumers. At every stage in this process, opportunities arise for the product to be contaminated, diverted, counterfeited, or otherwise adulterated. The Internet presents an additional layer of complexity by introducing more players into the system and more opportunities for criminals to harm patients.

FDA's role in addressing these threats is critical. FDA has undertaken a wide range of activities to harmonize international standards, to share scientific and technical expertise with our fellow regulators, to provide training around the world in crucial regulatory disciplines, and to design innovative risk modeling systems. The agency took aggressive action in the wake of the Heparin crisis to address the vulnerabilities that the incident exposed, including inspecting Heparin facilities and updating testing standards for the drugs.

We acknowledge that there is room for improvement, and we are doing all we can to address GAO's recommendations by stepping up our efforts to address globalization. In June, FDA published a special report, "Pathway to Global Product Safety and Quality," which lays out our global strategy and action plan.

The agency is developing a new operating model that relies on strengthened collaboration, improved information sharing and gathering, data-driven risk analytics, and the smart allocation of resources, leveraging the combined efforts of government, industry, and public and private sector third parties. Toward this goal, Commissioner Hamburg created a directorate focused on grappling with these challenges and appointed me to head that directorate.

Congress can help. Congress has the ability to align FDA statutory framework with the shift in the global paradigm. When President Franklin Delano Roosevelt established the modern FDA in 1938, the percentage of medical products imported into the United States was minimal.

Today the landscape is reversed. Nearly 40 percent of the drugs Americans take are imported and nearly 80 percent of the active pharmaceutical ingredients in those drugs are imported from more than 150 countries, many with less sophisticated manufacturing regulatory systems than our own. Only about one-third of the drug manufacturing facilities that FDA wants to inspect are in this country. The rest are spread around the globe.

New statutory authorities, which I detail more fully in my written testimony, can help to level the playing field between domestic manufacturers and their foreign counterparts, increase drug safety, and provide FDA with the information it needs to most effectively and efficiently oversee the global supply chain.

I appreciate your interest in this critical issue. I apologize for running over. But I look forward to working with you to address the challenges we face in protecting our Nation's health in this globalized world.

[The prepared statement of Ms. Autor follows:]

PREPARED STATEMENT OF DEBORAH M. AUTOR, J.D., ESQ.

INTRODUCTION

Good morning, Chairman Harkin and members of the committee. I am Deborah Autor, Deputy Commissioner for Global Regulatory Operations and Policy at the Food and Drug Administration (FDA or the Agency) in the Department of Health and Human Services (HHS). Thank you for the opportunity to discuss the safety of the American drug supply.

When President Franklin Delano Roosevelt established the modern FDA in 1938, the percentage of medical products imported into the United States was minimal. Today the landscape is reversed. Nearly 40 percent of the drugs Americans take are made elsewhere, and about 80 percent of active pharmaceutical ingredients (APIs) used in drugs manufactured in the United States come from outside our borders—from more than 150 countries, many with less sophisticated manufacturing and regulatory systems than our own. In addition to the sheer volume of imports and foreign facilities, there has been an increase in the variety of sources, shippers, methods of transportation and supply chain complexity of imported products, and our current authorities have not kept pace with the challenges of the current global marketplace. Combined, these factors create great challenges to FDA and industry in ensuring that all drugs are high quality and travel safely throughout their complex supply chains. These factors also provide opportunities for criminals to adulterate drugs for economic or other malevolent reasons.

When we refer to the drug supply chain, we are talking about the increasingly complex path that medical products travel, from raw source materials to finished products for consumers. At every stage in this process, opportunities arise for the product to be contaminated, diverted, counterfeited, or otherwise adulterated. The Internet presents an additional layer of complexity by introducing more players into the system and more opportunities for criminals to reach consumers. Our efforts to secure the supply chain both in the United States and abroad include minimizing risks that arise anywhere along the supply chain continuum, from sourcing a product's raw material, ingredients, and components through the product's manufacture, storage, transit, sale and distribution. A breach at any point in this continuum could lead to dangerous and even deadly outcomes for consumers. Supply chain safety threats also impact manufacturers' bottom lines due to costs associated with both recalls and decreased public confidence.

As members of this committee well know, this threat is not purely hypothetical. Recent incidents of adulteration, counterfeiting, and cargo theft have posed serious threats to public health. The consequences, throughout the world, have been tragic. In recent years, glycerin in fever medicine, cough syrup, and teething products was adulterated with the highly toxic solvent, diethylene glycol (DEG), resulting in the deaths of adults and children in Panama, and children in Haiti and Nigeria. Over the last 20 years, drug products containing glycerin contaminated with DEG have caused an estimated 570 deaths worldwide. Also in 2007, pet food adulterated with the industrial chemical melamine and cyanuric acid sickened several thousand pets in our country. The same contaminant was added to infant formula in China, fatally poisoning six babies and making 300,000 others gravely ill. Members of this committee are well aware of the 2008 heparin contamination crisis that resulted in several deaths and cases of serious illness.

Counterfeit drugs raise significant public health concerns, because their safety and effectiveness is unknown. A counterfeited drug could be made up of a substance that is toxic to patients. But even a non-toxic counterfeit drug with a substitute or no active ingredient could prove harmful to patients who take it, thinking that they are taking a lifesaving or life-sustaining medication. In 2003, over $20 million in illegally imported and counterfeit Lipitor, a popular cholesterol-lowering drug, was distributed throughout the United States. The source and manufacturing methods of the product were unknown and had the potential to endanger patients.

Cargo thefts of prescription drugs also pose a significant public health risk. In 2009 alone, an estimated 46 drug cargo thefts occurred, valued at a total of $184 million. These incidents are concerning to companies and consumers alike. Cargo thefts can cost drug manufacturers millions of dollars. They can also put consumers at risk because the stolen drugs may not have been stored or handled properly or may have been tampered with while outside of the legitimate supply chain. In March 2010, thieves broke into a warehouse and stole $75 million worth of prescription drug products, including chemotherapy, antidepressants, and blood-thinners. These products have not yet been recovered, and we fear they could be distributed, in spite of public warning. In 2009, stolen insulin was reintroduced into the drug

supply and caused adverse events in patients. The stolen insulin, which requires refrigeration, lost its potency and did not provide the needed glucose control.

In our increasingly complex and globalized world, additional authorities could be important tools to help support FDA's efforts to protect the safety of imports and the health of our citizens. New regulatory authorities may also help ensure that industry takes principal responsibility for the security and integrity of their supply chains and the quality control systems they use to produce medical products for the American people. FDA's efforts are also critical to ensuring product integrity. As such, we intend to further transform FDA over the next decade from a predominantly domestically focused Agency, operating in a globalized world, to an Agency fully prepared for a regulatory environment in which product safety and quality know no borders.

In June, FDA published a special report, "Pathway to Global Product Safety and Quality," our global strategy and action plan that will allow us to more effectively oversee the quality, safety, and efficacy of all products that reach U.S. consumers in the future. The Agency is developing a new, more global operating model that relies on strengthened collaboration, improved information sharing and gathering, data-driven risk analytics, and the smart allocation of resources, leveraging the combined efforts of government, industry, and public- and private-sector third parties. Toward this goal, FDA Commissioner Margaret Hamburg created a directorate focused on grappling with the truly global nature of today's world—food and medical product production and supply, as well as the science that undergirds the products we regulate—so that FDA can move from being a regulator of domestic products to one overseeing worldwide enterprises. She appointed me as Deputy Commissioner for Global Regulatory Operations and Policy to provide broad direction and support to FDA's Office of Regulatory Affairs and Office of International Programs, with a responsibility to address the challenges of globalization and import safety a top priority in the years to come and to ensure that we fully integrate our domestic and international programs to best promote and protect the health of the public. I appreciate the opportunity to testify before you in my new role and look forward to working together to address the challenges we face in protecting our Nation's health in this increasingly globalized world.

STEPS TO SECURE OUR NATION'S DRUG SUPPLY CHAIN

FDA has undertaken a wide range of activities aimed at addressing the challenges and opportunities of globalization, including efforts to harmonize scientifically rigorous standards internationally, to share scientific and technical expertise with our fellow regulators, to provide training around the world in crucial regulatory disciplines, to strengthen detection, surveillance and assessment systems, and to design innovative risk-modeling systems.

We now have permanent FDA overseas posts in Beijing, Shanghai, and Guangzhou, China; New Delhi and Mumbai, India; San Jose, Costa Rica; Mexico City, Mexico; Santiago, Chile; Brussels, Belgium; London, England; and Parma, Italy. This year, we have opened posts in Amman, Jordan and Pretoria, South Africa. These offices enable us to have a regional presence around the world and serve as important hubs for improved coordination with regulatory authorities and industry in other nations. They also conduct and facilitate inspections and other on-the-ground activities in foreign sites. We have more than 30 agreements with foreign counterpart agencies to share inspection reports and other non-public information that can help us make better decisions about the quality and safety of foreign products.

When governments collaborate to strengthen safety standards, the results are safer, higher-quality products and enhanced economic development through a productive industry and a strong, reliable export market. The arrangement is mutually beneficial. To a large extent, our success or failure in this effort will be contingent on the relationships we establish with our foreign partners. That is why we are working closely with our sister regulatory authorities, international and national organizations, and industry to leverage resources to accomplish FDA's mission. Especially in the area of good manufacturing practices for drugs, we already have agreed with major foreign counterparts on some harmonized international standards. By using the results of their inspections to assure us that their manufacturing plants are adhering to our agreed standard, we free up our inspectional resources to help ensure that such manufacturing practices are being followed in other, higher risk parts of the world. This also lessens the regulatory burden on industry, by allowing companies to manufacture to a common standard and to undergo fewer inspections by multiple authorities.

AFTER HEPARIN

The 2008 heparin contamination crisis is a case study in the vulnerabilities of the global supply chain. Heparin is a widely used injectable anticoagulant, derived from the mucosal tissue of pigs. In early 2008, contaminated heparin from China was associated with an increase in deaths in the United States. Whatever was contaminating this imported heparin could not be identified by the tests used at the time. After launching a far-ranging investigation, FDA scientists, working closely with academia and industry, developed a test methodology that identified a previously unknown contaminant in Chinese-manufactured heparin. The contaminated heparin contained over-sulfated chondroitin sulfate (OSCS), an intentionally added adulterant. An outbreak of blue ear pig disease had killed off a large portion of China's pig population, creating an incentive for criminals to seek an alternative that mimicked the chemical makeup of heparin but, tragically, proved dangerous to consumers.

FDA publicly referred to the heparin contamination crisis as a "wake-up call." It was an alert not only for FDA, but also for U.S. citizens, industry, and lawmakers about our dependence on a globalized drug supply and the key vulnerabilities in our drug supply chain. FDA has taken a number of significant steps to safeguard the U.S. supply of this medically necessary drug. The Agency invested considerable resources to inspect heparin manufacturing and testing facilities related to the supply of heparin in the United States. Additionally, the United States Pharmacopoeia, a standards-setting organization upon which FDA relies, now calls for the testing of heparin to detect the presence of OSCS, the contaminant that sickened patients in 2008. FDA has also implemented heparin-specific import surveillance including an import alert and multiple warning letters to ensure that adulterated heparin does not enter our borders.

But our efforts have not stopped there. The heparin crisis was a crime of opportunity, and we need to minimize these opportunities. We are committed to putting preventive measures in place that will protect American consumers from adulteration of all imported drugs. We combine risk-based approaches with sound scientific evidence to protect the public from adulterated and unsafe drugs. The Agency takes several factors into account in determining whether a particular drug ingredient may be at risk for adulteration. For example, when a drug ingredient depends on raw materials that are particularly expensive, criminals may have extra incentive to find a cheaper alternative to the expensive ingredient. If the cheaper alternative can mimic the chemical activity of the product and thereby go undetected by standard testing, as was the case in the heparin and melamine incidents, the risk of adulteration is higher. To date, FDA has systematically ranked more than 1,000 APIs in order of their respective risk of adulteration, based on a multi-factorial, risk-based model we developed. A subset of these higher-risk ingredients is targeted for additional sampling and special testing at the border. In addition, FDA is working to reduce the risk that counterfeit or adulterated drug products reach consumers in the U.S. market by developing standards for a track-and-trace system that would enable the identification of these products and facilitate efforts to recall them.

Through the creation of my position and other activities at the Agency, we have made addressing the challenges of globalization a top priority. To support this effort, FDA can benefit from new legislative authorities that are, at a minimum, commensurate with those of its major global counterparts.

DRUG SAFETY AUTHORITIES

In general, new regulatory authorities may help ensure that industry takes principal responsibility for the security and integrity of its supply chains and the quality control systems it uses to produce drugs for the American people. In an era of globalization, new authorities can help to level the playing field between domestic and foreign manufacturers, ensure product safety and provide FDA with the information it needs to protect consumers. Those authorities may include:

Leveling the Playing Field

• Refusal of product admission to the United States if inspection of the manufacturing facility is delayed, limited, or denied—this authority is critical to providing a strong incentive for foreign facilities to allow FDA to perform inspections and to permit FDA to exclude from domestic commerce products whose foreign manufacturers or facilities try to avoid subjecting themselves to the same requirements as domestic manufacturers and facilities. This authority is not currently explicit in FDA's law for any product other than foods.

• Require information upon importation—the Agency can refuse entry of an import that appears from examination of samples or otherwise to be adulterated or

misbranded, but FDA lacks authority to require certification or other assurance of compliance with applicable standards or requirements as a condition of importation, consistent with FDA's standards and requirements for the domestic drug supply. This is the opposite of the approach taken by many other countries, which place the burden on the importer or product owner to prove that its drug is compliant with country requirements.

• Quality management systems—FDA currently works with industry to ensure that individual companies have effective quality management systems in place; however, additional statutory authority could place greater responsibility on manufacturers to account for the quality and provenance of the materials that go into their products. This would level the playing field between the companies that work diligently on their quality management systems to provide high quality products, and those that do not.

• While FDA does not seek to interfere with regulatory authorities outside the United States, having express authority to address threats to U.S. consumers, whenever and wherever they may arise, is critical.

Increasing Drug Safety

• Mandatory recall authority—while in most instances firms eventually agree to voluntarily recall drugs that FDA believes pose a risk, FDA lacks the authority to compel such recalls and critical time can be lost in negotiations between FDA and a firm, leaving the public exposed to potentially serious health risks. The Agency currently has mandatory recall authority for medical devices, infant formula, and now many other foods, but not for drugs.

• Administrative destruction at the border—absent this streamlined authority, FDA is often forced to return violative products to their senders because the current process for destruction requires a hearing, which is time-consuming and costly. Foreign drugs can then find their way back to U.S. ports of entry several times, posing a potential threat to consumers and wasting critical resources that could be better spent identifying new threats. This authority would level the playing field for those who produce compliant products, whether located in the United States or abroad.

• Administrative detention—while FDA has the authority to administratively detain illegal foods and medical devices in U.S. commerce, it does not have a similar authority for drugs. Currently, we cannot immediately detain dangerous drug products when we find them. Absent this immediate tool, consumers can be exposed to unnecessary risks.

• Enhanced criminal and civil penalties for foreign and domestic suppliers—statutory changes could help to deter would-be criminals from targeting drug products, and bring FDA's penalties in line with those for other serious Federal health and safety violations.

Increasing Information

• Modernization of drug registration and listing—revising these statutory provisions may improve the timeliness, completeness, and accuracy of FDA's current registration and listing information, making sure FDA has accurate and up-to-date information about foreign and domestic parties involved in medical product manufacture.

• Notification to FDA—this authority would permit FDA to require foreign and domestic companies to provide complete information on threats such as counterfeiting, theft, non-compliance with regulatory standards, mislabeling or misbranding, or other threats to the security of the drug supply chain. Among other things, this would allow FDA to better spot emerging risks and trends across companies and then inform industry or take other proactive, preventive steps.

• Unique facility identifier—the absence of a system of unique drug facility identifiers, such as a D-U-N-S number, submitted to FDA both as a condition of registration and import, makes it difficult for FDA to properly follow threats up the supply chain and makes it more difficult to get different systems, including at different agencies, to properly cross-reference.

• Authority to share certain non-public information with other regulatory agencies and foreign governments—this authority would allow FDA to share certain information that could lead to timely identification, prevention, and resolution of emerging threats. Our ability to form global coalitions of regulators will be hampered if we cannot share critical information with our trusted partners.

• Track and trace—requiring a cost-effective track-and-trace system for all drug products throughout the supply chain would improve the security and integrity of the drug supply and ensure transparency and accountability of product manufacturing and distribution, whether the product is manufactured domestically or internationally.

In our increasingly complex and globalized world, these additional authorities represent important tools to help support efforts to protect the safety of imports and the health of our citizens.

CONCLUSION

Given the challenges and threats posed by an increasingly globalized marketplace, we must modernize our approach to drug safety. We appreciate the comments of Chairman Harkin and Ranking Member Enzi in July in support of including legislation in the reauthorization of the Prescription Drug User Fee Act (PDUFA) to address the challenges of globalization. We look forward to continuing to work together to achieve our shared goal of protecting American consumers. I would be happy to answer any questions.

The CHAIRMAN. Thank you very much, Ms. Autor. We'll start with rounds of 5-minute questions.

From your testimony, Ms. Autor, it sounds like one significant gap in our supply chain is FDA's limited ability to inspect foreign producers. What can be done to inspect these foreign facilities more frequently, given your limited resources?

Now, one of the things you mentioned in your written testimony—that I think you're asking Congress for—is the authority for the refusal of product admission to the United States if inspection of the manufacturing facility is delayed, limited, or denied. Is that one of the critical aspects of this?

Let's be honest about things. I believe FDA needs more personnel. I think FDA needs more money. But in the climate around here, I doubt that that's going to happen.

So on the one hand, we want more safety. We want to level the playing field. So you have offices right now—FDA has offices in China and India and places like that. I don't know how well they're staffed. I know the offices are there.

But speak to this—about inspections being delayed, about preannouncement of inspections—what good is it to do an inspection if you have to announce it 2 or 3 weeks in advance—and the ability of your offices overseas to conduct onsite inspections unannounced. Is that the kind of authority that you need from Congress?

Ms. AUTOR. Senator Harkin, you mentioned one authority in particular that would be very useful, which is the ability of FDA to refuse for import products from foreign facilities that have refused to let FDA in to inspect or delayed or denied an FDA inspection. It seems common sensical that if a company is not a good enough player to actually let the agency in to see how it's operating, those are not the products we want to come to the American consumers.

But at the moment, the law is not clear on our authority to do that. So that is very important.

With respect to being able to reach facilities overseas more, that's obviously very important. And we recognize, in this economy, our resources are going to continue to be an issue.

Our offices overseas are helpful. We have at this point 13 posts around the world, and they do some inspections. They do also a lot of work to collaborate and to work with our foreign counterparts, so that is part of the answer. And they are more likely than our U.S. inspectors to be able to make an unannounced inspection.

But in foreign countries, in particular, in China, there's a rule that we need to have a letter of invitation from the company before we can enter the country to inspect. So it's very difficult to do an unannounced inspection. And what that means is that the playing

field really is not level between the foreign manufacturers and the domestic manufacturers.

With the domestic manufacturers, we can show up at their door any day. They will usually let us in. If they don't, we can go and get a warrant and get in. On the foreign side, it's very hard to get there. When we get there, they may or may not let us in. If they do not let us in, we do not have the explicit authority to prevent the drugs from coming to U.S. consumers.

The CHAIRMAN. So taking China as an example, then, you have to have a letter of invitation from the company in order to be able to inspect. Is that right?

Ms. AUTOR. In order to get the visa to come to China to inspect. That's as I understand it.

The CHAIRMAN. I thought you have an office in China.

Ms. AUTOR. We do, and they do some inspections. They do some.

The CHAIRMAN. But do they have to have a letter of invitation?

Ms. AUTOR. I believe they do not. But I think it's not realistic to think that FDA will ultimately have enough personnel spread around the globe that we can see their facilities at all times when we want to. What it means is that we need to think creatively about how to assess the foreign——

The CHAIRMAN. So it's very clear that companies in China that manufacture ingredients or the finished drugs can thwart inspections, actually deny inspections, and still ship their product to the United States.

Ms. AUTOR. They can. And another interesting thing about our law is that it puts the burden on FDA to keep products out of the country. So if a manufacturer offers something for import, we have to show that something appears to be wrong with it in order to keep it out of this country.

Now, in every other grown-up country that we know of, the regulator has the authority to say, "If you want your product to come in, you must show us that your product is good." For us, we must show that it's bad. And when you think about that in the context of a globalized world where there are so many manufacturers we do not see, it's simply not a reasonable burden.

We simply think that manufacturers should be required to show some minimal standards that their product is approved, that it complies with good manufacturing practices in order to be able to access U.S. markets. And that will also level the playing field between the manufacturers who want to do it right and the manufacturers who don't.

The CHAIRMAN. I have one followup question. My time has expired. So I'll recognize Senator Enzi.

Senator ENZI. Thank you, Mr. Chairman.

The FDA still hasn't responded to my sole question for the record from our July hearing with the commissioner. I asked for a status report on the implementation of the GAO supply chain recommendations. I'll have several questions today that I'm sure I won't have time to ask.

Will you commit today to work with the committee in a more timely and responsive manner?

Ms. AUTOR. Absolutely, Senator Enzi. I do understand that you have questions for the record pending related to our GAO rec-

ommendations, that those questions came in in August, and we are working very hard to respond to them. We want to make sure we get the technical facts right before we send them to you. And when we respond, you will see that we have continued to make serious progress against the challenges and the issues that GAO has pointed out.

Senator ENZI. Good. FDA promulgates current and good manufacturing practices, or GMPs, to tell companies how to manufacture drugs. Given the risks of globalization, why hasn't the FDA updated its know-your-suppliers GMPs?

Ms. AUTOR. There are some opportunities we have to update our standards under current law. And we will try to do so if Congress does not update the law. But updating the requirements through regulation is a lengthy, uncertain, expensive process for the taxpayers, essentially litigious, with an unclear outcome.

So the GAO, I think, has said that it's urgent for these issues to be resolved. I think if Congress believes these issues are also urgent, then Congress can help to resolve them quickly through legislation.

Senator ENZI. Even if we do legislation, won't you still have to go through the regulatory process with it?

Ms. AUTOR. I think that depends on what the legislation says. I think there are some things which you may be able to do immediately through legislation, which would change the paradigm, which would bring manufacturers up to a higher level or level the playing field between the good players and the bad players, between the domestic ones and the international ones. There's some things where we would have to do regulations afterwards.

But to get our statute up to a modern, globalized world—I think that's something that Congress could be able to do quickly.

Senator ENZI. Since we should be working on that quickly, I hope you would get the specific things to us so that we can do that and perhaps avoid the regulation route, although I think there's a big hesitancy to do anything too specific by a group of people that don't work on it on a daily basis.

So GAO found that 83 percent of the time, FDA does not target foreign drug inspections on the basis of risk. FDA's "Pathway to Global Product Safety and Quality" reported earlier this year said the agency is building intelligence, surveillance, and risk assessment programs to fix this problem. To what extent have you implemented these programs?

Ms. AUTOR. Well, the "Pathway to Global Product Safety and Quality" report was issued in June, and part of implementing that report is my new position in the new directorate, and I assumed my job on July 31. So I haven't had a tremendous amount of time to establish global coalitions and global data systems yet, but we are thinking very hard about how we can do that.

As you pointed out, the "Pathway" report talks about global data systems, advanced risk analytics, as well as global coalitions of regulators and reliance on public and private third parties. And we believe that this is the way for FDA to do the best it can within today's current challenges.

We have some history in collaborating with our foreign regulators, for example, on drug inspections with Europe and on active

pharmaceutical ingredients with Australia and Europe. So there are steps we've taken in the past which lead us to this path, and we are serious about implementing it right now. And I'm doing my best to get it started, and I haven't done so over the past 6 weeks.

Senator ENZI. I appreciate your efforts on that. The GAO says that FDA does not have adequate information systems to detect overseas supply chain risks. In 2009, FDA started migrating out of a paper-based system called DRLS into an electronic system called E-LIST.

According to GAO, FDA says it can't tell whether the system change has helped solve the problem or made it worse. What is the status of that system migration?

Ms. AUTOR. We have implemented an electronic registration and listing system, and I think it's been very helpful. It has eliminated some of the possibility for human error when we literally had people typing in what they received on forms in the mail. So that's a major improvement bringing us into this century, I believe. And it has helped us to establish consistency in our records, because we don't have that error.

We are also doing other things which we think can help with our data systems. For example, we are working with Dun and Bradstreet on a unique facility identifier. And one thing that you could think about legislatively is requiring facilities to have a unique identifier, such as the D-U-N-S number, because having a unique facility identifier for drug manufacturers greatly helps FDA's ability to have a clear inventory. We don't have the possibility of typographical errors in addresses.

We have Dun and Bradstreet's database of millions of corporate entities to verify our information. We can work together with our foreign counterparts, because we can use the same consistent numbering system and compare our records. There's a great deal we have done in implementing the electronic system, and there's a great deal we can do to improve that, especially with some help from Congress.

Senator ENZI. I'd raise a few more questions, but my time has expired.

Thank you, Mr. Chairman.

The CHAIRMAN. Thank you, Senator Enzi.

Now, in order of arrival, Senator Bennet, then Senator Roberts, then Senator Franken.

Senator Bennet.

STATEMENT OF SENATOR BENNET

Senator BENNET. Thank you, Mr. Chairman, and the Ranking Member for holding this very important hearing.

As I travel around the State, I hear a lot about regulation. People are asking all the time about regulation. Sometimes people say, "We should get rid of all that," and sometimes people have a different point of view.

If there was ever a case that screamed out for a bipartisan approach to get us into, as Ms. Autor was just talking about, the 21st Century, it is this case, because there are twin objectives, I think, that we need to accomplish somehow as we go forward here. One is to recognize that 80 percent, as you said, of our active ingredi-

ents are now produced overseas and are largely unregulated, and we don't know what's going on there, which is a shock to Coloradans when they hear that, just as it's a shock when they hear that the GPS in their car is more advanced than the ones in our airplanes because of our inability to deal with the FAA bill.

The other piece is that we have got to figure out, as we're doing this, how to create a competitive biosciences industry here in the United States, one that we can rely on in the 21st Century to create jobs in places like Colorado. And I appreciate very much that Commissioner Hamburg came out to Colorado to have a conversation with our bioscience community and to work collaboratively with them.

I'm interested to hear a little bit, generally, about how you see the globalization of our drug supply fitting into the overall effort to remove regulatory barriers and to inspire innovation right here in the United States.

Ms. AUTOR. Sure. Thank you, Senator Bennet. I would say right now that the incentives are not really there for innovation in quality. And what we hope that Congress will look at is quality management systems which will improve innovation and quality, foster innovation and quality. Right now, because the playing field is unlevel, it does not reward companies who want to do it right, who want to find innovative ways to do it right.

And I should point out, by the way, that doing it right does not necessarily cost more. We have one company, for example, who committed to their quality side of the house, to making sure their manufacturing was right. And so they spent $100 million less than they had intended to spend on quality.

Conversely, companies who don't do it right or companies that run into problems can lose an awful lot of money. In the Heparin crisis, Baxter lost $30 million in sales and $4.7 billion in market capitalization. Recently, we had recalls of injectable products because there was glass shearing off inside the vials. So there were glass lamellae in the vials, which obviously can't be injected into patients. Industry spent probably $250 million recalling those products.

So that's money that they're spending on cleaning up quality issues rather than investing in new products and being innovative. So we think actually that leveling the playing field and putting in place a modern system can help a great deal in innovation and competitiveness.

Senator BENNET. And one of the things I hear all the time from the folks in our State that are in this field is that other countries also are having to grapple with this question as well and are modernizing their regulatory agencies to deal with it, being more responsive than they've historically been. And I wonder if you could talk in that context a little bit about something else you mentioned in your testimony, which was the harmonization of the international regime.

Are there ways that we can rely on others to help us do this work, and others rely on us to help us do this work? How do we make sure that we've got a global regulatory system that can actually manage this problem?

Ms. AUTOR. By all means. And the "Pathway to Global Product Safety and Quality" report, I think, makes crystal clear FDA's recognition that we simply can't do it alone and that we need to work together with our counterparts, that we need to form global coalitions of regulators. To some extent, that means harmonizing standards. To some extent, it means simply being able to rely on each other.

And this has great benefits for industry as well. It leads to fewer inspections, streamlined requirements, and if we're able to reach more companies around the world, it effectively minimizes what we have now, which is a competitive advantage of noncompliance.

Companies who choose to skirt the law can do so beyond regulators' reach and thereby make more money by doing it poorly. Working together with our counterparts, harmonizing and collaborating, is a way that we can level that playing field and we can improve quality overall.

Senator BENNET. And that, I think, is one of the reasons why the good actors in this world want these statutes updated and want this regulatory regime updated, because if there's a bad actor, it hurts everybody in the entire industry and our patients as well.

Thank you for your testimony.

[The prepared statement of Senator Bennet follows.]

PREPARED STATEMENT OF SENATOR BENNET

Mr. Chairman, it's been more than 70 years since the laws governing the Nation's pharmaceutical industry were updated. The year was 1938. Franklin D. Roosevelt was president, gas cost 10 cents a gallon, and the average price for a new home was $3,900.

A lot has changed. Unfortunately, the country's drug safety laws haven't. Many regulations are woefully, and dangerously, outmoded, in the face of an increasingly globalized and opaque supply chain that is vulnerable to theft and criminal activity.

So buyer beware.

The blood thinner heparin, for example, used in your local hospital, may originate from pig intestines stored on the floor of a grimy factory in a remote region of China. Diabetes patients may be oblivious to the fact that their insulin—which requires refrigeration—may have been stolen by a street gang, left out in the heat, then sold back into the market.

In 1938, drug manufacturers were easily checked for quality and safety. The lines of commerce consisted mostly of the 48 contiguous States. Regulators were able to inspect drug manufacturers every 2 years or show up unannounced to verify ingredients with relative ease.

Today, up to 80 percent of all drug ingredients are manufactured in countries like China or India. In some cases, drug makers buy ingredients from foreign suppliers without actually knowing who those suppliers are. As a result, products show up on our shelves that do not meet basic U.S. safety standards—and put American families at risk.

Three years ago, for example, contaminated heparin led to hundreds of illnesses and several deaths. The contaminant was traced to a filthy, uninspected and infested factory in China.

We should consider as an issue of national security the path pharmaceuticals take before and once they enter our country. Hundreds of different hands distribute and repackage drugs before they appear on our pharmacy shelves and in our hospitals. Our system's lack of transparency makes it almost impossible to know who is actually handling our medicine.

You can get more data from a barcode on a gallon of milk than you can from a bottle of aspirin two aisles over. We need a system to ensure that drugs can be tracked like a FedEx package—to help us more easily spot counterfeits or detect stolen or recalled products.

Accountability must stretch across the entire supply chain—all the way to distribution.

Right now, each State has different laws for tracking drugs. Compare that to airport security. If every major U.S. airport had different airport security processes, with some easier to flout, imagine which one a terrorist would prefer.

A comprehensive, practical approach will increase safety, help efficient interstate commerce and minimize inconsistencies among the current patchwork of State requirements.

I introduced the Drug Safety and Accountability Act last year, to increase both industry and regulatory controls to ensure drug safety and protect patients. It would require more accountability of drug company ingredients across the entire supply chain. It also requires that the Food and Drug Administration fix its inadequate monitoring systems on manufacturing sites here and abroad, while giving the agency authority to order a drug recall—a power that 94 percent of Americans want the agency to have.

The FDA needs resources to improve accountability and quality. To its credit, industry has been willing to consider user fees—whether domestic or international—so that the agency can do the number and scope of inspections that we need.

Equally important, we need to increase penalties for those who game the system. Right now, you get higher penalties for illegally copying a DVD than for counterfeiting drugs. Criminals who once specialized in dealing illegal narcotics are now gravitating toward counterfeiting pharmaceutical drugs—because penalties are so much weaker.

As Congress begins to consider FDA reauthorization, it must work across party lines to address these supply-chain shortcomings.

A strong drug supply and distribution chain that protects U.S. consumers should not be a partisan issue. It is a matter of competitiveness, national security and consumer safety.

Thank you.

Thank you, Mr. Chairman.

The CHAIRMAN. Thank you very much, Senator Bennet.

And I want to note again for the record that Senator Bennet has introduced legislation on this last year.

I was reading it over in preparing for this hearing today, and I thought you made one point in your remarks on introducing the bill that we get more information from the barcode on a gallon of milk than we do on——

Senator BENNET. Right.

The CHAIRMAN [continuing]. Anything we get from the drugs that we get. I thought that really kind of capsulized it.

Senator Roberts.

STATEMENT OF SENATOR ROBERTS

Senator ROBERTS. Well, thank you, Mr. Chairman. And I echo the comments of my colleague and friend from Colorado.

I'm still somewhat confused, which is a state that I walk around in a lot, and I don't know exactly what you want in terms of new authority. Could you clarify that for me? Does the FDA really need new authorities to inspect the foreign facilities, or are you simply asking for more funds, or both? I mean, there's a difference between a need and a want, and in the climate we're in, it's extremely difficult in regards to funding. But authority may be the answer. And Senator Enzi really posed that question, so my question is just a repeat of his.

Ms. AUTOR. Sure. Well, just to clarify, we're not talking about new authorities to allow us to inspect foreign facilities, per se. What we're talking about is new authorities in light of the fact that our pharmaceutical supply chain has globalized. So, for example, as I said, right now, if a foreign facility refuses to let us inspect—and we need to let their products in. Globalization has greatly increased—or it may need to—the law is unclear as to whether we can keep their products out simply because they refused inspection.

Globalization has greatly increased the challenges for the agency, greatly increased the opportunities for counterfeiting, contamination, drug diversion——

Senator ROBERTS. Yes, ma'am. I understand that. But do you want new authority or not?

Ms. AUTOR. Yes, sir.

Senator ROBERTS. You do want authority?

Ms. AUTOR. Yes, sir, and I'm talking about——

Senator ROBERTS. And you will respond to Senator Enzi and the Chairman's specific questions. OK. We got that down. Thank you. I didn't mean to interrupt you, and I apologize.

Can you really provide the committee with a full and complete list of all the foreign drug establishments that are involved in the U.S. drug supply chain? Is that possible?

Ms. AUTOR. If you want the long list, we could try to do that. I think that we do have lists of the facilities who offer products for import to the United States.

Senator ROBERTS. Right.

Ms. AUTOR. And lists of the foreign facilities that register with us, which is a requirement.

Senator ROBERTS. Well, that would really help, I think, in understanding the breadth of the current problem. You've outlined a serious situation.

Last year, stolen insulin managed to make its way back onto the pharmacy shelves and reached patients. As you know, this is a heat sensitive product that will not work if improperly stored. I don't know how this deception was possible. There is no comprehensive national system, apparently, to track and authenticate packages of drugs as they travel from the manufacturer to the wholesaler to the pharmacy.

What steps can the FDA take to help the transparency of the drug distribution? And do you need any authority or an additional mandate to do that?

Ms. AUTOR. Yes, sir. As you pointed out, products are able to infiltrate the legitimate supply chain at this time, including products like the stolen Levemir insulin.

Senator ROBERTS. Right.

Ms. AUTOR. What we would need to rectify that would be a requirement for a track-and-trace system, a system which allowed manufacturers and pharmacies to know who had touched the drug between the time it was manufactured and the time it reached the pharmacy. Right now, under the law, we are required to come up with a national standard, but the law does not say that that standard is enforceable, or that it's a violation of the law not to comply with the standard, or that that law will pre-empt the requirements of the States.

And the risk is right now, in fact, that what will happen is the 50 States will each put in separate requirements leading to a patchwork which will be very difficult for industry——

Senator ROBERTS. Yes, that would be a hodge-podge for sure. But you do have a plan for the transparency, in fact, if you had the authority and you had the funds to do it. Where are you with that?

Ms. AUTOR. We are working on a track-and-trace standard. We don't have the authority to make it enforceable. We do have the standard to put it out there and to hope that people follow it.

Senator ROBERTS. I see. OK. I'm going to touch on what the Senator from Colorado said. Like the Senator from Colorado and like the Chairman and like Senator Enzi, everywhere I go, people say, "What on earth are you doing passing regulations that are crazy and are about to put me out of business? What are you guys doing?" I always reply and say, "I'm an us guy, not a you guy." And then I try to trace the regulation back that doesn't make much sense.

When it finally reaches downstream—we were talking about upstream, but now this is downstream—and it's in every conceivable business that is essential to the committee. Let's talk about the pharmacists.

The pharmacists today in my State do not serve Medicare patients because of all of the regulations with PPACA and the new healthcare law, and also competitive bidding, and they can't sell durable medical equipment, and they can't do this or that. And some of them are going out of business because of the regulatory overkill.

I want to know about the potential cost to the individual pharmacist, especially in rural and small town America, if we implement a full track-and-trace program. Somebody's got to pay for this, and the consumer usually does, and then it—well, until it gets to the consumer—it goes to the pharmacist. So I'm worried about the small town pharmacy. You won't have a problem with any kind of drug if you don't have a pharmacist to distribute it in a local town, because they won't get any.

Ms. AUTOR. Yes. Sir, we fully understand that, and we understand the concerns about pharmacies, about the economic impact of a track-and-trace system. And we are committed to trying to come

up with the best system we can, balancing the need to protect public health with the need to be able to allow businesses to remain economically viable. We are trying to do that.

We held a public meeting. We had the docket open so we could collect comments. We are considering those comments and trying to come up with the best model that allows us to have the maximum impact with a minimum burden.

I would point out in 2009, we had $184 million in drug cargo thefts. So that is an economic loss to the industry and to the pharmaceutical community, which ultimately gets passed on to consumers and probably the pharmacies as well as a cost. So we need to come up with a system that works best, balancing all of those interests.

Senator ROBERTS. So you do have a cost-benefit yardstick in your closet. I appreciate it. Thank you.

I'm over time, Mr. Chairman. Pardon me.

The CHAIRMAN. Thank you, Senator.

Senator Franken.

STATEMENT OF SENATOR FRANKEN

Senator FRANKEN. Thank you, Mr. Chairman, and thank you and the Ranking Member for this very important hearing.

Let me ask about the Heparin. That came from China and Baxter was the—distributed it here in this country? Is that right?

Ms. AUTOR. Virtually all Heparin in this country comes from China because it takes one pig to make one vial of Heparin. And, frankly, there are a lot of pigs in China to be able to make the Heparin, so most of the Heparin in this country comes from China. In that case, we traced the contaminated Heparin back to China, and then it was distributed through Baxter and other companies in the United States.

Senator FRANKEN. Can you comment on whether FDA has considered requiring manufacturers, as opposed to the FDA, to hold sub-suppliers and others further down the chain accountable? That would, I think, put the responsibility on the Baxters of this world to say, "Look, you know, I've got to check the drugs I'm distributing."

Ms. AUTOR. Yes, by all means. And, in fact, when we've talked about quality systems and something that Congress might want to look at, one of the things we talked about is the manufacturer should have adequate control over their suppliers and over their supply chain. And right now, a lot of good companies do that. But the problem is that there are companies that do not, and what we need to do is raise the floor so that we have consistent quality throughout.

But, by all means, the idea is that manufacturers are best placed to be able to ensure the quality of their products. They know what the risks are associated with those products. They can make sure that they've thought about the vulnerabilities. They can make sure that they have audited the suppliers. By all means, I think it's not something that the agency could even realistically do. It's for manufacturers to do. But it's something that needs to be clear in the law that they need to do that.

Senator FRANKEN. Can the FDA inform the public of which companies are doing it and which ones aren't?

Ms. AUTOR. One thing that the FDA does now, which we started doing recently, is we post our inspectional outcomes for manufacturers. So we think that's one thing that helps to bring a little bit of transparency to who's doing it right and who isn't. I think that's the most helpful kind of thing we can do.

But, again, to have a system which, in light of globalization, requires all manufacturers to do it right in the first place is very helpful, because consumers often don't get a choice about which drug they take. They go to the pharmacy and they give them what they get. So the importance is to make sure that when the drugs get there, they are the adequate quality for consumers.

Senator FRANKEN. Yes, but, I mean, the pharmacist would be the one, I would think, that would be looking at what manufacturers are doing, the inspection of the subcontractors, and then the pharmacist would be more inclined to take the product of the companies that are acting in good faith.

Ms. AUTOR. Perhaps, if they have that flexibility, they would do that. But more important, I think, is to make sure that the manufacturers do it right in the first place.

Senator FRANKEN. How do you do that?

Ms. AUTOR. I think you make sure to put in place a statutory scheme which levels the playing field between the good guys and the bad guys, puts enough requirements in place to do that. Also, the other things that Congress could think about are things that would enhance product safety, like a mandatory recall system, like increased criminal penalties relating to adulterating drugs, and also things that increase information.

So FDA's best role in the circumstance, I think, is to be able to look across industry to see emerging risks. But right now, for example, if a company has a counterfeiting incident or a cargo theft or contamination, in most cases they're not required to tell us. So we may not only be able to immediately jump in on that issue to protect the public health and investigate, but if it's something which other parts of the industry know about, we cannot tell them if we're not alerted.

There are situations where companies have voluntarily told us, "We have a problem. There's a contamination of our inactive ingredients," and we've said to other companies, "You need to be on the lookout with respect to this inactive ingredient so that you can protect yourselves." But absent a statutory scheme, we can't consistently play that role, which I think is the best role for us.

Senator FRANKEN. Let me ask about your ability to inspect foreign subcontractors. Is there anything in our trade laws, in our trade policies, where we can enforce that? In other words, if you're going to be selling your drugs and your ingredients of drugs here in the United States, we insist that we be able to inspect your factories. Can that be in part of our trade policy and the World Trade Organization's policies?

Ms. AUTOR. As far as I know, that's not something that's likely to happen. I'm not a trade expert, but the challenge, I think, is that imposing barriers to trade is very difficult through those kinds of organizations.

But what we're talking about differently is the ability to, under the Federal Food, Drug, and Cosmetic Act, under FDA's act, say, "If you have refused, delayed, or denied inspection, then your product won't come in." And that, by the way, is an authority the Congress put in place recently for food safety. So it's something that can be easily done through our act. The same thing, saying to companies, "You need to show something that's good about your product if you want to come into the United States" rather than making FDA show there's something bad about it, is a way to very quickly change the paradigm to keep up with globalization in a way that is really imperative.

Senator FRANKEN. OK. Thank you.

Thank you, Mr. Chairman.

The CHAIRMAN. Thanks, Senator.

Senator Mikulski.

STATEMENT OF SENATOR MIKULSKI

Senator MIKULSKI. Thank you, Mr. Chairman.

Ms. Autor, I'm so glad to see you. Know that being here at this hearing, I've got several hats, one of which, of course, is a Senator from Maryland in which FDA is headquartered. And we're so proud of the work you do under the difficult circumstances, funding, and contradictory requirements that you're given.

But I'm also here as a member of the Intelligence Committee, and I'm also here as the appropriator for the Commerce Justice Department, meaning Justice work, because I believe that adulterated drugs coming into this country is criminal. I think it's a form of murder. You cannot rely on blood thinners the way members of my own family have, be a diabetic and rely on prescription drugs, and not know that which you are ingesting in your body could be the very thing that kills you rather than the very thing that saves you from a stroke, a heart attack, or a diabetic coma.

So we've got to get real. We've got to get serious, and we have to have a sense of urgency. That's not laying it on FDA. That's laying it on us. We throw zillions at DOD to protect the homeland, to fight them over there so they don't kill us here. We've got to have that same attitude toward those that are adulterating drugs over there, quite frankly, so they don't kill us here.

Now, your background is terrific. You're a trial lawyer. You worked at the Justice Department. You have an incredible background in working with Federal law enforcement.

My question to you is, what are we going to do to create this sense of alarm, alarm, a red alert, going to the edge of our chair, DEFCON 3, because this is a growing problem. This is not exaggerated hyperbole for CNN for me. This is a compelling need when we look at the number of people who take prescription drugs, in which we are now so vulnerable and which are usual and customary drugs, particularly the issue of blood thinner.

Now, I don't know about those Chinese pigs. OK? I don't know if they're communist pigs. I don't know if they're capitalist pigs, and I don't know if they're clean pigs in order to do this. But what I do know is that right now, all over the United States of America, there are a million—over a million people taking some form of blood thinner, that depends on Heparin and then to Warfarin.

So my question to you is are we moving with that sense of urgency? Has this been escalated to a homeland security issue? Is this the top of anyone's agenda? Because this is as important as protecting our borders as we do from anything else illegal or threatening coming into our country.

Ms. AUTOR. Thank you for that question. I really appreciate it. And I really do share your sense of urgency. I worry about products like this, which, frankly, cross our border every day. This is counterfeit Tamiflu and counterfeit Lipitor, and you're welcome to look at it if you'd like. They look very, very similar, and they come into this country.

And one important thing that your question gets to, Senator Mikulski, is the fact that the risk to the pharmaceutical supply chain is not simply from people who are out to make a buck. There is a risk from people who have much more malevolent motivations, and I think we need to be aware of that.

And so I do everything I can to reach global facilities, to change what we're doing at the agency, to be more proactive, to be more creative, to collaborate. But there are things which are not currently in the law, like requiring manufacturers—clearly requiring manufacturers to update their test standards to look for vulnerabilities.

Senator MIKULSKI. Especially making criminal charges, exactly.

Ms. AUTOR. Yes.

Senator MIKULSKI. I mean, really, we've got to do some out-of-the-box thinking here. It's not are you for regs or against regs, you know. We are for smart regulation.

Ms. AUTOR. I completely agree. And with respect to another crisis like Heparin or something worse, it's not a matter of if. It's a matter of when.

Senator MIKULSKI. Now, let's talk about FDA, Justice, and the Department of Homeland Security. Do they feel that this has this heightened urgency? And has this been moved up the chain of command while we're looking at the supply chain of drugs and counterfeit drugs?

Ms. AUTOR. That's a very interesting question. I can't speak for them. I'm not sure I could answer that question sitting here today. But I'd be happy to answer that for you.

Senator MIKULSKI. Well, you know what? I just wanted our committee to know this. Senator Whitehouse is on the Intel Committee. So is Senator Roberts. We see the growing nexus between organized crime, international organized crime, and the corruption of public officials, overlooking any other kinds of collaborative enforcement. So I don't want to do complicated foreign policy here, but I think we need to look at it.

I know my time is up. I had a chance to talk with Interpol this summer and do extensive conversations about their digital databases and what they see as a growing problem. This is an international problem, so it is not only for us. Whatever we feel about harmonization or not and the EU and all of that, the fact is that for any of us who value safety and efficacy, this is, I think—has to be elevated to a national security, homeland security, and criminal level. I look forward to talking with my colleagues so that we

approach it that way, so that the American people know that if they take it, it will be OK.

Thank you.

The CHAIRMAN. Senator Mikulski, thank you very much. I just want to follow up. Our witness from the Pew Charitable Trust will be testifying later—Mr. Coukell. And his testimony I read last night said that this incident—he's talking about the Heparin incident, Senator Mikulski—said that the Heparin incident resulted in 150 deaths. But to this day, no one in any country has yet been held accountable.

Is that a fact, Ms. Autor? Can you verify that or not? I'm just reading from what someone's going to testify here shortly that said that no one has yet been held accountable in any country.

Ms. AUTOR. With respect to Heparin, we did conduct a criminal investigation in China but, ultimately, were not able to bring that to fruition at this point with a—finding a culpable individual. One thing I would say about Heparin, though, is it's a crime of opportunity. It was a crime of opportunity. So even catching the person who did that wouldn't solve the problem. What we need to do is work to minimize the opportunities for something like that to happen again.

The CHAIRMAN. Thank you very much.

Senator Whitehouse.

STATEMENT OF SENATOR WHITEHOUSE

Senator WHITEHOUSE. Thank you, Chairman.

Ms. Autor, you said about inspecting overseas facilities that manufacture product for American consumers that you—I think you used the phrase, may not be able to prevent the importation of a drug manufactured in a facility that refused inspection. What are the dimensions of that question, that you may not be able to? Why is that an uncertain proposition, and what are the—sort of, from a lawyer's point of view—what are the weasel words around that proposition that define it a little bit more clearly?

Ms. AUTOR. Sure. The way the law works right now is we have to show that the product appears to be adulterated, misbranded, or unapproved in order to keep it out of the country. Again, the burden is on us, and that is our standard.

So the argument we have to make is that because they refused inspection or delayed or limited our inspection, that means that their products appear to be adulterated or misbranded or unapproved. That's an argument we can make. It's not as clear in the law as it could be, especially if Congress wants to clearly say, "We recognize that there are a lot of global facilities out there, and we want to level the playing field and make sure that we assure the quality of the products being imported."

Senator WHITEHOUSE. So it's a largely fact-based determination, case by case——

Ms. AUTOR. Right.

Senator WHITEHOUSE [continuing]. With you evaluating whether you'll be able to succeed and——

Ms. AUTOR. Exactly. We have to—in every situation, at a minimum, we would have to say, "Here are the facts. This is the facility. Here's where we tried to contact them. Here's what we did"—

as opposed to simply saying, "They didn't let us in." Clearly, if they didn't let us in, we shouldn't let them in.

Senator WHITEHOUSE. You indicated that you thought that the smartest and simplest way to go about this would be to allow the American companies to police this themselves with adequate supply chain assurance policies. You said that most of the bigger companies had adequate, good supply chain assurance policies, but there were some players that did not.

What is your authority to regulate the supply chain assurance policies as a target that is, in effect, a proxy for your ultimate determination, which is whether or not the drug is safe? Can you actually say to American industries, "We want to review your supply chain assurance policy. If you don't have one that we think is up to snuff, then you're in violation," and force behavior that way? Do you have that regulatory authority?

Ms. AUTOR. That authority is not as clear as it could be under the law. That is something that Congress could clarify. At this point, we can look to putting out regulations on that, but that's a lengthy, uncertain, potentially litigious, and very costly process for the American people.

Senator WHITEHOUSE. How close have you come in the past? Can you think of any examples of regulations that you have done that oversee an internal process questioning the company as a means of determining whether the ultimate product is safe? Or would this be venturing into completely new territory?

Ms. AUTOR. We have good manufacturing practice regulations in place which do some of that. But those were written in 1978 before the real explosion of global manufacturing. So they don't get to that as clearly as they could. And so it's not new territory, but it's something that Congress, I think, could deal with much more quickly if you share our urgency about this problem.

Senator WHITEHOUSE. OK. Thank you very much.

Thank you, Mr. Chairman.

The CHAIRMAN. Senator Blumenthal.

STATEMENT OF SENATOR BLUMENTHAL

Senator BLUMENTHAL. Thank you, Mr. Chairman, and thank you for holding this hearing on this very important topic.

Thank you for being here today and for your good work. You referred just a few minutes ago to a crime of opportunity in Heparin. And I want to talk about what creates opportunities for crime, in fact, exponentially increasing crime in theft or illegal importation. And in my view, one of the main contributors—one of the main circumstances that creates that opportunity is the acute shortages of certain drugs in this country arising from a variety of circumstances and problems, one of them being termination of the legitimate supply, but also others being the gray market.

The gray markets that have been documented in this country for certain drugs literally are threatening our health. The gray markets are playing Russian roulette with patients lives, and shortages of drugs around the country mean that hospitals are unable to meet the demand for workhorse medicines.

I'm using that phrase because it's been used to me by hospital administrators, doctors, emergency room physicians—workhorse

medicines that provide basic anesthesia, cancer treatment—these are not exotic or unusual drugs. Often they are generics where the profit motive has dissipated or disappeared, and so shortages occur, or the result of hoarding.

And as you are aware, I'm sure, in April 2011 Premier Healthcare Alliance asked its pharmacy support team to review the incidence of gray market offers, and they found overall 1,745 examples of gray market offers recorded in 42 acute care hospitals with an average markup of 650 percent. So the impacts are not only on health. They are on safety and on cost. Healthcare delivery is increasingly costly because of the gray markets and shortages that are the result of defects in the current supply chain.

So all of that said, I wonder if you could address what steps can be taken. And there is a group of Senators, myself included, working to combat the acute shortages of certain drugs. What can FDA do under its existing authority?

Ms. AUTOR. Sure. Thank you for the question. That's a lot of different issues. Let me speak to one thing first, which is what creates the opportunities for things like the Heparin crisis. And that's really more players involved in the drug supply chain, greater volume of products imported, greater number of firms involved, greater complexity of supply chain, greater complexity of the products, further and further foreign manufacturers. So that's with respect to Heparin.

With respect to shortages, that is really a complex economic problem, I believe, primarily. There are fewer manufacturers who have consolidated their drug manufacturing to fewer facilities, fewer lines, for products for which the economics are not great because they're not very highly priced products anymore. They have not fully invested in the quality of those products.

The agency takes the problem very seriously. We are doing what we can to prevent it. Last year, for example, when we were notified of shortages early, we were able to prevent 38 different shortages because we were told early. We could work with the manufacturers to see if the products were good enough to go to patients, to work with creative solutions, like, for example, if a product had metal shavings in injectable products, at one point, we worked with the company to send a filter so that the product could still be used in patients.

We are also working toward having a public meeting with stakeholders to talk about this. But it really is a multifaceted problem that requires a multifaceted solution and all of the stakeholders to step up to the plate.

With respect to gray market, that's a real concern. Shortages create an incentive and an opportunity for people to, at best, charge an awful lot for these products, at worse, introduce counterfeit or contaminated products. One of the things that would really help with that, frankly, is a track-and-trace system, because the pharmacies and hospitals would be able to know if this product being offered to them from these new sources at high prices was, in fact, legitimate product, because they would know everybody who had touched it throughout the supply chain.

Senator BLUMENTHAL. My time has expired. I would welcome an opportunity to follow up with you and your staff on this issue, par-

ticularly as to those 38 instances that you mentioned and what we can learn from them and maybe the others where there was no action and what we can learn from them as well.

Does the FDA need additional authority for track-and-trace?

Ms. AUTOR. Yes. We would need additional authority to make it clear that we can promulgate enforceable standards for track-and-trace, also to require manufacturers to notify us of shortages. Right now, the authority on that is limited. So if we know about shortages, we can try to prevent them. It's not—we can't always do it, but at least knowing about them in advance helps us to deal with the problem.

Senator BLUMENTHAL. Track-and-trace wouldn't be a solution to shortages.

Ms. AUTOR. It would not be a solution to shortages, but it would be something to address some of the public health risks associated with shortages.

Senator BLUMENTHAL. Thank you.

Thank you, Mr. Chairman.

The CHAIRMAN. Thank you very much.

We have to get on to our second panel, but I just briefly wanted to ask one question, Ms. Autor, and that is, most of the testimony and most of the discussion today has to do with prescription drugs. Could you just briefly address yourself to the over-the-counter drug supply? Do the same problems accrue there? And also to the use of excipients—that's a word that I didn't know about until I got into this area—the inactive ingredients, which, going clear back to the 1930s, ethylene glycol, was one of those. Can you address the risks both to the over-the-counter drug supply and also to the inactive ingredients that go into drugs and the problem that you may see in both those areas?

Ms. AUTOR. Yes, by all means. One of the ways I tend to look at the pharmaceutical supply—because I've been working in this area for so long—is to think about sort of the innovative products, the generic products, the over-the-counter products, and the components. All of them present similar but different challenges.

For example, I would say the generics industry, by talking to us about a user fee package, I think, has recognized some of the challenges inherent with generic drugs and with respect to our ability to police the supply chain in general. Over-the-counter drugs present a challenge because most of them are done through a monograph system, essentially a cook book system for a price, that don't require in those cases affirmative FDA approval.

If they follow our rules for what has to be in there and how they're labeled, etc, then they can come on the market. That means that there's a greater opportunity for firms to introduce products without us knowing. And those products could go straight from, frankly, a facility in China we've never seen to a pharmacy in any State.

So that is a real challenge, and that's why we talk about really needing to understand the global supply chain and really needing to put in, in particular, authorities at the border to stop those products and say, "Show us there's something right about your products before they come in."

Excipients also present a real challenge. Those are inactive ingredients, essentially. And as you pointed out, diethylene glycol is one that's led to 570 deaths worldwide in the last 20 years and 100 deaths in this country in 1937, leading to passage of FDA's law. So there's a huge number of excipients out there, and they're used in a lot of different products. The same thing used in drugs might also be used in foods.

So that's why we talk about the need for manufacturers to be responsible for policing their supply chain, because it will never be the case, frankly, that FDA can go to all those facilities and assure they're doing everything right. It has to be incumbent upon a manufacturer who's selling pharmaceuticals that people rely on to save their lives to go and make sure that their components are satisfactory.

The CHAIRMAN. Thank you very much, Ms. Autor. We have Senators that want to submit some questions in writing to you.

Thank you very much for being here and thanks for your testimony.

Ms. AUTOR. Thank you.

The CHAIRMAN. Now we'll call our second panel up. I'll introduce them as they take their places at the table. First, starting from my left, we have Dr. Marcia Crosse, Director of Health Care for the GAO, Government Accountability Office. She's been at GAO since 1983, so she comes to us today with significant experience in evaluating public health issues. Her work focuses, in particular, on evaluating areas such as biomedical research, product safety, and pharmaceutical regulations.

Next we have Ms. Kendra Martello, the assistant general counsel for the Pharmaceutical Research and Manufacturers of America, otherwise we know as PhRMA.

And we appreciate your being here.

Next is Mr. Gordon Johnston, senior advisor for Regulatory Sciences at the Generic Pharmaceutical Association. He has worked in the pharmaceutical industry for the past 25 years, and was formerly the Deputy Director of the FDA's Office of Generic Drugs.

We thank you for being here.

Mr. Martin VanTrieste—I hope I pronounced that correctly—senior vice president of Quality at Amgen and past chair of the Rx-360, a pharmaceutical supply chain consortium. As a past chair of Rx-360, Mr. VanTrieste led industry members in creating objectives to better share information regarding counterfeit and adulterated materials in the pharmaceutical supply chain.

We thank you for being here.

And last is Allan Coukell. Did I pronounce that right?

Mr. COUKELL. Coukell, sir. Thank you.

The CHAIRMAN. Allan Coukell, the director of medical programs at the Pew Health Group. He oversees Pew's initiatives related to pharmaceutical supply chain safety. In July, the Pew released an interesting report that shed new light on the weaknesses and gaps in our pharmaceutical supply chain.

And we thank you for being here.

All of your testimonies will be made a part of the record in their entirety. And I'll go from left to right and ask if you can sum up in 5 to 7 minutes. I appreciate it.

We'll start with you, Dr. Crosse.

STATEMENT OF MARCIA CROSSE, Ph.D., DIRECTOR, HEALTH CARE, GOVERNMENT ACCOUNTABILITY OFFICE, WASHINGTON, DC

Ms. CROSSE. Thank you, Mr. Chairman, Ranking Member Enzi, and members of the committee. I'm pleased to be here today to discuss FDA's oversight of the drug supply chain.

Over the past several years, GAO has issued a number of reports on the challenges we identified in FDA's oversight of drugs that are manufactured in other countries for the U.S. market. While FDA is making progress, we have concerns about the agency's use of information and the pace at which it is implementing changes.

Globalization has placed new demands on FDA as the pharmaceutical industry has increasingly relied on global supply chains in which each manufacturing step may be outsourced to foreign establishments. In examining these issues, we have particularly focused on the challenges for FDA in inspecting these facilities, the limitations on FDA's knowledge and information about these facilities, and the steps FDA is taking to improve its oversight of the supply chain.

Inspections of foreign drug manufacturers are an important element of oversight. As we've heard, FDA is far from achieving foreign inspection rates comparable to domestic inspection rates where the agency is required to conduct inspections every 2 years.

To frame this with some numbers, in 2008, we reported that it would take FDA about 13 years to inspect the foreign establishments that were then on its inventory. Since that time, FDA has been increasing the number of foreign inspections it performs, reducing the estimated time to inspect all establishments to about 9 years. However, while the agency is trying to catch up, it's facing a continually growing number of foreign facilities.

In addition, although FDA has been working to develop risk information to help it prioritize its foreign inspections, the risks of the products being manufactured have not been the real drivers of which facilities are inspected. Rather, foreign establishments have generally only been inspected when they have been named on an application for a new drug.

Conducting inspections abroad also continues to pose unique challenges for the agency. For example, FDA cannot require foreign manufacturers to allow it to inspect their facilities, and logistical issues preclude FDA from conducting unannounced inspections as it does for domestic establishments.

In addition to the challenges of conducting inspections, we previously reported that FDA lacked complete and accurate information about these facilities, information critical to understanding the supply chain. FDA databases contain incorrect information, and the agency still does not have an accurate list of the foreign establishments manufacturing drugs for the U.S. market. This hampers FDA's ability to make inspection decisions and adequately oversee shipments arriving at our ports.

The contaminated Heparin crisis provides a useful case study of some of the problems FDA is facing, including facilities that had never been inspected, mix-ups in FDA's databases, outdated testing

standards, questions about manufacturers' validation of their supply chains, delays in gaining entry because of visa requirements, FDA's inability to require cooperation by foreign facilities, difficulties tracing contaminated supplies to end products including medical devices, and difficulties in recalling products thought to be contaminated.

Given the difficulties that FDA has faced in overseeing the supply chain and recognizing that more inspections alone are not sufficient to meet the challenges posed by globalization, the agency has begun to implement other initiatives to improve its oversight. As we've heard today, FDA established new offices overseas and has taken other positive steps, such as collaborating and exchanging information with foreign governments and developing systems that would assist its oversight of products at the border.

FDA should be credited for its recent actions which represent important initial steps toward addressing these challenges. However, as the agency has acknowledged, there are additional steps that it still needs to take.

We have previously made recommendations to address some challenges such as poor information and planning, and the agency has identified additional authorities that could provide it with necessary enforcement tools. In light of the growing dependence upon drugs manufactured abroad and the potential for harm, FDA needs to act quickly to implement changes across a range of activities in order to better assure the safety and availability of drugs for the U.S. market.

Mr. Chairman, Ranking Member Enzi, this concludes my prepared remarks. I'd be happy to answer any questions that you or other members of the committee may have.

[The prepared statement of Dr. Crosse follows:]

PREPARED STATEMENT OF MARCIA CROSSE, PH.D.

SUMMARY

HIGHLIGHTS—WHY GAO DID THIS STUDY

Globalization has placed increasing demands on the Food and Drug Administration (FDA) in ensuring the safety and effectiveness of drugs marketed in the United States. The pharmaceutical industry has increasingly relied on global supply chains in which each manufacturing step may be outsourced to foreign establishments. As part of its efforts, FDA may conduct inspections of foreign drug manufacturing establishments, but there are concerns that the complexity of the drug manufacturing supply chain and the volume of imported drugs has created regulatory challenges for FDA. FDA has begun taking steps to address some of these concerns, such as the establishment of overseas offices.

This statement discusses (1) FDA's inspection of foreign drug manufacturing establishments, (2) the information FDA has on these establishments, and (3) recent FDA initiatives to improve its oversight of the supply chain. The statement presents findings based primarily on GAO reports since 2008 related to FDA's oversight of the supply chain. These reports include *Food and Drug Administration: Overseas Offices Have Taken Steps to Help Ensure Import Safety, but More Long-Term Planning Is Needed* (GAO–10–960, Sept. 30, 2010) and *Drug Safety: FDA Has Conducted More Foreign Inspections and Begun to Improve Its Information on Foreign Establishments, but More Progress Is Needed* (GAO–10–961, Sept. 30, 2010). GAO supplemented this prior work with updated information obtained from FDA in August and September 2011.

DRUG SAFETY—FDA FACES CHALLENGES OVERSEEING THE FOREIGN DRUG MANUFACTURING SUPPLY CHAIN

WHAT GAO FOUND

Inspections of foreign drug manufacturers are an important element of FDA's oversight of the supply chain, but GAO's prior work showed that FDA conducts relatively few such inspections. In 2008, GAO reported that in fiscal year 2007 FDA inspected 8 percent of foreign establishments subject to inspection and estimated that, at that rate, it would take FDA about 13 years to inspect all such establishments. GAO recommended that FDA increase the number of foreign inspections it conducts at a frequency comparable to domestic establishments with similar characteristics. FDA subsequently increased the number of foreign establishment inspections. FDA's inspection efforts in fiscal year 2009 represent a 27 percent increase in the number of inspections it conducted, when compared to fiscal year 2007—424 and 333 inspections, respectively. However, FDA officials acknowledged that FDA is far from achieving foreign drug inspection rates comparable to domestic inspection rates—the agency inspected 1,015 domestic establishments in fiscal year 2009. Also, the types of inspections FDA conducts generally do not include all parts of the drug supply chain. Conducting inspections abroad also continues to pose unique challenges for the agency. For example, FDA faces limits on its ability to require foreign establishments to allow it to inspect their facilities. Furthermore, logistical issues preclude FDA from conducting unannounced inspections, as it does for domestic establishments.

GAO previously reported that FDA lacked complete and accurate information on foreign drug manufacturing establishments—information critical to understanding the supply chain. In 2008, GAO reported that FDA databases contained incorrect information about foreign establishments and did not contain an accurate count of foreign establishments manufacturing drugs for the U.S. market. FDA's lack of information hampers its ability to inspect foreign establishments. GAO recommended that FDA address these deficiencies. FDA has taken steps to do so, but has not yet fully addressed GAO's concerns.

Given the difficulties that FDA has faced in inspecting and obtaining information on foreign drug manufacturers, and recognizing that more inspections alone are not sufficient to meet the challenges posed by globalization, the agency has begun to implement other initiatives to improve its oversight of the drug supply chain. FDA's overseas offices have engaged in a variety of activities to help ensure the safety of imported products, such as training foreign stakeholders to help enhance their understanding of FDA regulations. GAO recommended that FDA enhance its strategic and workforce planning, which FDA agreed it would do. FDA has also taken other positive steps, such as developing initiatives that would assist its oversight of products at the border, although these are not yet fully implemented. Finally, FDA officials identified statutory changes that FDA believes it needs to help improve its oversight of drugs manufactured in foreign establishments. For example, in place of the current requirement that FDA inspect domestic establishments every 2 years, officials indicated the agency would benefit from a risk-based inspection process with flexibility to determine the frequency with which both foreign and domestic establishments are inspected. In light of the growing dependence upon drugs manufactured abroad and the potential for harm, FDA needs to act quickly to implement changes across a range of activities in order to better assure the safety and availability of drugs for the U.S. market.

Chairman Harkin, Ranking Member Enzi, and members of the committee, I am pleased to be here today to discuss the Food and Drug Administration's (FDA) oversight of the Nation's drug supply chain.[1] Globalization has placed increasing demands on FDA, which is responsible for the oversight of drugs marketed in the United States, regardless of whether they are manufactured in foreign or domestic establishments.[2] While Americans once used drugs that were mostly manufactured

[1] Drugs are defined to include, among other things, articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease, and include components of those articles. 21 U.S.C. § 321(g)(1)(B), (D).

[2] FDA regulations define manufacturing to include the manufacture, preparation, propagation, compounding, or processing of a drug. 21 CFR § 207.3(a)(8) (2011). In addition, FDA regulations define an establishment as a place of business under one management at one general physical location. 21 CFR § 207.3(a)(7) (2011). Drug manufacturers may have more than one establishment.

domestically, this is no longer the case. According to FDA, the number of drug products manufactured at foreign establishments has more than doubled since 2002, with China and India accounting for the greatest shares of this growth. In addition, the pharmaceutical industry has increasingly relied on global supply chains in which each manufacturing step may be outsourced to foreign establishments. The complexity of the drug supply chain, the volume of imported drugs, and the number of foreign establishments producing these drugs have created regulatory challenges for FDA. The danger associated with an insecure supply chain was highlighted in January 2008, when FDA responded to a crisis involving the contamination of the active pharmaceutical ingredient (API) used to manufacture heparin,[3] a medication used to prevent and treat blood clots. The contaminated heparin, which was associated with numerous adverse events—including deaths—came from a facility in China. During its investigation, FDA determined that some manufacturers were not adequately safeguarding their heparin supply chains.[4]

In recent years we have reported on several aspects of FDA's ability to protect Americans from unsafe and ineffective drugs entering our supply chain.[5] Amidst growing concerns with the increasing demands placed on the agency, including its ability to ensure the quality of drugs manufactured overseas, we added FDA's oversight of medical products to our High-Risk Series.[6] FDA has acknowledged that globalization has fundamentally changed the environment for regulating pharmaceutical products and the agency has begun taking steps to address some of these concerns, such as the establishment of overseas offices.[7]

My remarks today will focus primarily on information collected for several reports we issued since 2008 that specifically cite concerns we identified related to FDA's oversight of the manufacturing side of the supply chain for drugs produced by overseas establishments for marketing in the United States.[8] Specifically, I will discuss (1) FDA's inspections of foreign drug manufacturing establishments, which are intended to assure that the safety and quality of drugs are not jeopardized by poor manufacturing practices; (2) the information FDA has on these establishments; and (3) recent FDA initiatives to improve its oversight of the supply chain.

For our work reviewing FDA's inspections of foreign drug manufacturing establishments, we obtained and analyzed FDA data on foreign and domestic drug manufacturing establishment inspections conducted from fiscal years 2007 to 2009. We also examined methods used by FDA to select establishments for inspection. For our work examining how FDA responded to the heparin crisis, we reviewed actions FDA took during the crisis period, which FDA defined as January 2008 through May 2008. We also interviewed FDA officials and drug manufacturers and reviewed FDA documents, such as inspection reports and internally produced summaries (e.g., a time line of events related to the crisis).

For our work reviewing the information FDA has on foreign drug manufacturing establishments, we obtained data from FDA's registration database on the number

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[3] An API includes any component of a drug that is intended to provide pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease. See 21 CFR § 210.3(b)(7) (2011). In this statement, we refer both to drug products—drugs in their finished dosage form—and to APIs as "drugs."

[4] The heparin supply chain starts with a raw source material, primarily derived from the intestines of pigs, that is processed into crude heparin. Thousands of small pig farms in Chinese villages extract and process pig intestines in small workshops called casing facilities. Consolidators collect different batches of heparin from various workshops and sell these batches to manufacturers, who further refine the crude heparin into heparin API, the active ingredient used in heparin drug products and heparin containing devices. More than half of the finished heparin products in the United States and globally are made from Chinese-sourced materials.

[5] See the *Related GAO Products* page at the end of this statement.

[6] GAO, *High-Risk Series: An Update*, GAO–11–278 (Washington, DC: February 2011). We first added FDA's oversight of medical products to our High-Risk Series in January 2009.

[7] In late 2008 and early 2009, FDA established overseas offices comprised of staff covering particular countries or regions. FDA has staff located overseas in Beijing, Shanghai, and Guangzhou, China; New Delhi and Mumbai, India; San Jose, Costa Rica; Mexico City, Mexico; and Santiago, Chile. In June 2011, FDA also located staff in Amman, Jordan and Pretoria, South Africa.

[8] GAO, *Drug Safety: Better Data Management and More Inspections Are Needed to Strengthen FDA's Foreign Drug Inspection Program,* GAO–08–970 (Washington, DC: Sept. 22, 2008); GAO, *Food and Drug Administration: Overseas Offices Have Taken Steps to Help Ensure Import Safety, but More Long-Term Planning Is Needed,* GAO–10–960 (Washington, DC: Sept. 30, 2010); GAO, *Drug Safety: FDA Has Conducted More Foreign Inspections and Begun to Improve Its Information on Foreign Establishments, but More Progress Is Needed,* GAO–10–961 (Washington, DC: Sept. 30, 2010); and GAO, *Food and Drug Administration: Response to Heparin Contamination Helped Protect Public Health; Controls That Were Needed for Working With External Entities Were Recently Added,* GAO–11–95 (Washington, DC: Oct. 29, 2010).

of establishments registered to market their drugs in the United States.[9] We also obtained data from FDA's import database on the number of establishments that have manufactured drugs that were shipped to the United States.[10] We reviewed FDA's initiatives for improving the accuracy of the agency's data on foreign establishments contained in these databases, which are both used to manage the foreign drug inspection program.

For our work reviewing recent FDA initiatives intended to improve the agency's oversight of foreign drug manufacturing establishments, we reviewed documentation and interviewed FDA officials from each of FDA's five overseas offices to learn about their activities, challenges, accomplishments, and strategic and workforce planning. For three of the overseas offices—China, India, and Latin America—we interviewed office staff and others, such as officials from FDA's foreign regulatory counterparts, during on-site visits in February and March 2010. We also reviewed documents related to the agency's efforts to augment its existing information on foreign drug establishments, such as information obtained from foreign regulatory authorities. We supplemented that prior work with updated information that we received from FDA in August and September 2011.

We conducted the work for the performance audits on which this statement is based from September 2007 to September 2008, June 2009 to September 2010, and from August to September 2011 for selected updates. Our work was conducted in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

BACKGROUND

As part of its efforts to ensure the safety and quality of imported drugs, FDA may conduct inspections of foreign establishments manufacturing drugs, including APIs, that are imported into the United States. FDA relies on these establishment inspections to determine compliance with current good manufacturing practice regulations (GMP).[11] The purpose of these inspections is to ensure that foreign establishments meet the same requirements as domestic establishments to ensure the quality, purity, potency, safety, and efficacy of drugs marketed in the United States.

Requirements governing FDA's inspection of foreign and domestic establishments differ. Specifically, FDA is required to inspect every 2 years those domestic establishments that manufacture drugs in the United States, but there is no comparable requirement for inspecting foreign establishments that market their drugs in the United States.[12] However, drugs manufactured by foreign establishments that are offered for import may be refused entry to the United States if FDA determines—through the inspection of an establishment, a physical examination of drugs when they are offered for import at a point of entry, or otherwise—that there is sufficient evidence of a violation of applicable laws or regulations.[13]

FDA conducts two primary types of drug manufacturing establishment inspections. Preapproval inspections of domestic and foreign establishments may be conducted before FDA will approve a new drug to be marketed in the United States. In addition, FDA conducts GMP inspections at establishments manufacturing drugs already marketed in the United States to determine ongoing compliance with laws and regulations.

FDA CONDUCTS RELATIVELY FEW INSPECTIONS OF FOREIGN DRUG ESTABLISHMENTS

Although inspections of foreign drug manufacturing establishments—which are intended to assure that the safety and quality of drugs are not jeopardized by poor manufacturing practices—are an important element of FDA's oversight of the supply chain, our previous work has shown that FDA conducts relatively few inspections

[9] Domestic and foreign establishments that manufacture drugs for the U.S. market are required to register annually with FDA. 21 U.S.C. § 360(b), (i)(1).

[10] FDA's import database contains information on drugs and other FDA-regulated products offered for entry into the United States, including information on the establishment that manufactured the drug.

[11] GMPs provide a framework for a manufacturer to follow to produce safe, pure, and high-quality drugs. See 21 CFR pts. 210, 211 (2011). See also International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, *ICH Harmonised Tripartite Guideline: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients Q7* (Geneva, Switzerland: Nov. 10, 2000).

[12] See 21 U.S.C. § 360(h), (i)(3).

[13] See 21 U.S.C. § 381(a).

of the establishments that it considers subject to inspection. Specifically, in our 2008 report, we estimated that FDA inspected 8 percent of such foreign drug establishments in fiscal year 2007. At this rate, we estimated that it would take FDA about 13 years to inspect all foreign establishments the agency considers subject to inspection. In 2010, we reported that FDA had increased its inspection efforts in fiscal year 2009. We estimated that FDA inspected 11 percent of foreign establishments subject to inspection and it would take FDA about 9 years to inspect all such establishments at this rate. FDA's inspection efforts in fiscal year 2009 represent a 27 percent increase in the number of inspections the agency conducted when compared to fiscal year 2007—424 and 333 inspections, respectively[14] In contrast, FDA conducts more inspections of domestic establishments and the agency inspects these establishments more frequently. For example, in fiscal year 2009, FDA conducted 1,015 domestic inspections, inspecting approximately 40 percent of domestic establishments. We estimated that at this rate FDA inspects domestic establishments approximately once every 2.5 years. To address these discrepancies, we recommended that FDA conduct more inspections to ensure that foreign establishments manufacturing drugs currently marketed in the United States are inspected at a frequency comparable to domestic establishments with similar characteristics.[15] FDA agreed that the agency should be conducting more foreign inspections, but FDA officials have since acknowledged that the agency is far from achieving foreign drug inspection rates comparable to domestic inspection rates and, without significant increases to its inspectional capacity, the agency's ability to close this gap is highly unlikely.[16]

In addition to conducting few foreign drug manufacturing inspections, the types of inspections FDA conducts generally do not include all parts of the drug supply chain. For example, FDA officials told us during our review of the contaminated heparin crisis that the agency typically does not inspect manufacturers of source material[17]—which are not required to be listed on applications to market drugs in the United States—and generally limits its inspections to manufacturers of the finished product and APIs. Furthermore, once FDA conducts an inspection of a foreign drug manufacturer, it is unlikely that the agency will inspect it again, as the majority of the foreign inspections FDA conducts are to inform decisions about the approval of new drugs before they are marketed for sale in the United States.

Despite increases in foreign drug establishment inspections in recent years, FDA continues to face unique challenges conducting inspections abroad. Specifically, as we identified in our 2008 report on FDA's foreign drug inspections, FDA continues to experience challenges related to limits on the agency's ability to require foreign establishments to allow the agency to inspect their facilities.[18] For example, while inspecting establishments in China during the heparin crisis, Chinese crude heparin consolidators refused to provide FDA full access during inspections—in particular, one consolidator refused to let FDA inspectors walk through its laboratory and refused FDA access to its records. As a result, FDA officials said they focused on the manufacturers' responsibilities to ensure that these establishments could trace their crude heparin back to qualified suppliers that produce an uncontaminated product and requested that manufacturers conduct their own investigations of any heparin products for which they received complaints or that did not meet specifications. Furthermore, FDA faces other challenges conducting foreign inspections, such as logistical issues that necessitate the agency notifying the manufacturer of the agency's intention to inspect the establishment in advance. In contrast to domestic inspections which are conducted without prior notice, FDA contacts foreign manufacturers prior to inspection to ensure that the appropriate personnel are present and that the establishment is manufacturing its product during the time of the inspection. In some cases, FDA must obtain permission from the foreign government of the country in which an establishment is located in order to conduct an inspection. FDA officials report that inspections may be conducted several months after an establishment has been notified of FDA's intent to conduct an inspection due to the need to obtain visas and other delays. As a result of such advance notice, FDA staff

[14] FDA attributes this increase in fiscal year 2009 foreign drug inspections to staffing changes—the creation of a drug inspection cadre and the placement of investigators overseas—and increased resources dedicated to these types of inspections.

[15] See GAO–08–970.

[16] We noted in our September 2010 report that, in response to our inquiries and those of congressional staff, FDA had undertaken a review to determine the appropriate inspection frequency for foreign and domestic drug establishments. However, as of September 2011, this review had not been completed.

[17] For example, in the case of the heparin supply chain, the source material is primarily derived from the intestines of pigs, which is processed into the crude heparin that is refined into heparin API.

[18] See GAO–08–970.

conducting inspections may not observe an accurate picture of the manufacturer's day-to-day operations.

FDA LACKS COMPLETE INFORMATION ON FOREIGN DRUG ESTABLISHMENTS

Our previous reports indicated that FDA has experienced challenges maintaining complete information on foreign drug manufacturing establishments. This lack of information, which is critical to understanding the supply chain, hampers the agency's ability to inspect foreign establishments. In 2008, we reported that FDA did not maintain a list of foreign drug establishments subject to inspection, but rather the agency relied on information from their drug establishment registration and import databases to help select establishments for inspection.[19] However, we found that these databases contained incorrect information about foreign establishments and did not contain an accurate count of foreign establishments manufacturing drugs for the U.S. market. For example, in our 2008 report, we identified that for fiscal year 2007, FDA's registration database contained information on approximately 3,000 foreign drug establishments that registered with FDA to market drugs in the United States, while the import database contained information on about 6,800 foreign establishments that offered drugs for import into the United States.[20] Some of the inaccuracies in the registration database reflected the fact that, despite being registered, some foreign establishments did not actually manufacture drugs for the U.S. market.[21] Additionally, the inaccurate count of establishments in the import database was the result of unreliable manufacturer identification numbers generated by customs brokers when a drug is offered for import.[22] As a result of these inaccuracies, FDA did not know how many foreign establishments were subject to inspection. To address these inaccuracies, we recommended that FDA enforce the requirement that establishments manufacturing drugs for the U.S. market update their registration annually and establish mechanisms for verifying information provided by the establishment at the time of registration.

Since then, FDA has taken steps to address these deficiencies and improve the information it receives from both the registration and import databases, though these efforts have not yet fully addressed the concerns we raised in 2008. For example, in June 2009, FDA began requiring all drug establishments marketing their products in the United States to submit their annual registration and listing information electronically, rather than submitting the information on paper forms to be entered into the registration database. FDA indicated that, as of September 2011, the implementation of this requirement has eliminated the human error that has been associated with the transcription of information from paper forms to electronic files. As part of electronic registration, FDA has also requested that each establishment provide a unique identification number—a Dun and Bradstreet Data Universal Numbering System (D-U-N-S®) Number[23]—as a way to help avoid duplications and errors in FDA's data systems.[24] In addition, in September 2011, FDA officials reported that the agency had begun to take steps to enforce its annual registration requirement. They indicated that FDA will now conduct outreach to establishments that have not submitted an annual registration to confirm that they are no longer producing drugs for the U.S. market or to ensure they register, as required, if they are continuing to manufacture drugs for the U.S. market. They said that if an establishment does not respond to FDA's outreach, it is to be removed

[19] See GAO–08–970.

[20] In our 2010 report, we indicated that, in fiscal year 2009, FDA's import database contained information for about 7,000 foreign establishments, compared with the approximately 3,200 foreign drug establishments that were registered with FDA in that year. See GAO–10–961.

[21] Such establishments may have gone out of business, but not informed FDA, or the establishments may not actually ship drugs to the United States. Some foreign establishments may register with FDA, but never ship drugs to the United States. FDA officials told us that such foreign establishments may register because, in foreign markets, registration may erroneously convey an "approval" or endorsement by FDA.

[22] As we reported in 2010, the algorithm used by customs brokers to assign the manufacturer identification number does not provide for a number that is reliably reproduced or inherently unique. Consequently, according to FDA officials, multiple records may be created for a single establishment, resulting in an inflated count of the number of establishments. See GAO–10–961.

[23] The D-U-N-S® Number is a unique nine-digit sequence recognized as the Federal Government's universal standard for identifying and keeping track of business entities. Submitting the site-specific number for an entity would provide, by reference to the number, certain business information for that entity that is otherwise required for drug establishment registration.

[24] Additionally, FDA, in conjunction with 20 of the nearly 50 Federal agencies involved in the oversight of products imported into the United States, supports efforts for Customs and Border Protection—which control the implementation of this proposal—to adopt unique establishment identifiers for all establishments whose products, including drugs, are imported into the United States.

from the registration database. To further address concerns with the import database, FDA has an initiative underway to eliminate duplicate information by taking steps to identify and remove all duplicate drug establishment records from existing import data over the next few years.

RECENT FDA INITIATIVES TO IMPROVE OVERSIGHT OF THE SUPPLY CHAIN

Given the difficulties that FDA has faced in inspecting and obtaining information on foreign drug manufacturers, and recognizing that more inspections alone are not sufficient to meet the challenges posed by globalization, the agency has begun to explore other initiatives to improve its oversight of the drug supply chain. We reported that FDA's overseas offices had engaged in a variety of activities to help ensure the safety of imported products. These included establishing relationships with foreign regulators, industry, and U.S. agencies overseas; gathering information about regulated products to assist with decisionmaking; and, in China and India, conducting inspections of foreign establishments.[25] Although we noted that the impact of the offices on the safety of imported products was not yet clear, FDA staff, foreign regulators, and others pointed to several immediate benefits, such as building relationships. However, they also described challenges related to some of their collaborations with domestic FDA offices and the potential for increasing demands that could lead to an unmanageable workload. We reported that FDA was in the process of long-term strategic planning for the overseas offices, but had not developed a long-term workforce plan to help ensure that it is prepared to address potential overseas office staffing challenges, such as recruiting and retaining skilled staff. We recommended that FDA enhance its strategic planning and develop a workforce plan to help recruit and retain overseas staff and FDA concurred with our recommendations. In September 2011, FDA indicated that it had developed a 2011 to 2015 strategic plan and was in the process of updating it, and it had initiated a workforce planning process.

FDA has also implemented collaborative efforts with foreign regulatory authorities to exchange information about planned inspections as well as the results of completed inspections. In December 2008, FDA, along with its counterpart regulatory authorities of the European Union and Australia, initiated a pilot program under which the three regulators share their preliminary plans for and results of inspections of API manufacturing establishments in other countries. For example, FDA could receive the results of inspections conducted by these regulatory bodies and then determine if regulatory action or a followup inspection is necessary. FDA contends that prospectively sharing this information could allow these regulatory bodies to more efficiently use their resources by minimizing the overlap in their inspection plans. According to agency officials, the agency had used inspection reports from the other regulators to improve its knowledge of a small number of API manufacturing establishments, most of which had not been inspected in the last 3 years, but that it was interested in inspecting due to a pending drug application.

FDA has also taken other steps to improve the information that the agency maintains on foreign establishments shipping drugs to the United States. In August 2008, FDA contracted with two external organizations to implement the Foreign Registration Verification Program. Through this program, contractors conduct site visits to verify the existence of foreign establishments that are registered with FDA and confirm that they manufacture the products that are recorded in U.S. import records.[26] According to FDA officials, establishments that are new to the U.S. market or are importing products not typically manufactured at the same establishment are considered candidates for the verification program.[27] For example, FDA officials told us about an establishment that was selected for the program because, according to agency records, it was offering for import into the United States pickles and an API—two products not normally manufactured at the same establishment. As of September 2011, the contractors had visited 142 foreign drug establishments located in Asia, Australia, Africa, Canada, and Europe, 27 of which did not appear to exist at the address provided by the establishments at the time of registration.[28] Accord-

[25] We also reported that FDA overseas officials had started to provide training, responses to queries, and other assistance to foreign stakeholders to help them improve their regulatory systems and better understand FDA regulations.

[26] According to FDA officials, the Foreign Registration Verification Program covers establishments manufacturing all FDA-regulated products.

[27] To select establishments for the Foreign Registration Verification Program, FDA uses information from its import database to determine the products that establishments are shipping to the United States and to identify establishments that are importing a variety of products.

[28] According to FDA, the agency has engaged contractors to conduct at least 125 more such visits of foreign drug manufacturing establishments during the coming year.

ing to FDA, the agency uses the information obtained from the contractors as screening criteria to target drug products from those establishments for review at the border.[29]

FDA is also developing initiatives that would assist its oversight of products at the border. For example, FDA is in the process of establishing its Predictive Risk-based Evaluation for Dynamic Import Compliance Targeting (PREDICT) import screening system. The system is intended to automatically score each entry based on a range of risk factors and identify high-risk items for review. FDA piloted this system on seafood products in the summer of 2007. FDA determined that the system expedited the entry of lower-risk products, while identifying a higher rate of violations among products that were tested when they were offered for import. The agency planned to have the system implemented in all locations and for all FDA-regulated products by June 2011, although its deployment has been delayed. According to FDA, full deployment of PREDICT is currently slated for December 2011.

FDA also identified statutory changes that would help improve its oversight of drugs manufactured in foreign establishments. These include authority to (1) suspend or cancel drug establishment registrations to address concerns, including inaccurate or out-of-date information; (2) require drug establishments to use a unique establishment identifier; and (3) implement a risk-based inspection process, with flexibility to determine the frequency with which both foreign and domestic establishments are inspected, in place of the current requirement that FDA inspect domestic establishments every 2 years.

CONCLUDING OBSERVATIONS

Globalization has fundamentally altered the drug supply chain and created regulatory challenges for FDA. In our prior reports we identified several concerns that demonstrate the regulatory difficulties that FDA faces conducting inspections of, and maintaining accurate information about, foreign drug establishments. While inspections provide FDA with critical information, we recognize that inspections alone are not sufficient to meet all the challenges of globalization. FDA should be credited for recent actions, such as collaborating with and exchanging information on drug establishments with foreign governments, that represent important initial steps toward addressing these challenges. However, as the agency has acknowledged, there are additional steps that it still needs to take. We have previously made recommendations to address some challenges, such as poor information and planning, and the agency has identified additional authorities that could provide it with necessary enforcement tools. In light of the growing dependence upon drugs manufactured abroad and the potential for harm, FDA needs to act quickly to implement changes across a range of activities in order to better assure the safety and availability of drugs for the U.S. market.

Chairman Harkin, Ranking Member Enzi, and members of the committee, this concludes my prepared statement. I would be pleased to respond to any questions you may have at this time.

RELATED GAO PRODUCTS

High-Risk Series: An Update. GAO–11–278. Washington, DC: February 2011.

Food and Drug Administration: Response to Heparin Contamination Helped Protect Public Health; Controls That Were Needed for Working With External Entities Were Recently Added. GAO–11–95. Washington, DC: October 29, 2010.

Drug Safety: FDA Has Conducted More Foreign Inspections and Begun to Improve Its Information on Foreign Establishments, but More Progress Is Needed. GAO–10–961. Washington, DC: September 30, 2010.

Food and Drug Administration: Overseas Offices Have Taken Steps to Help Ensure Import Safety, but More Long-term Planning Is Needed. GAO–10–960. Washington, DC: September 30, 2010.

Food and Drug Administration: FDA Faces Challenges Meeting Its Growing Medical Product Responsibilities and Should Develop Complete Estimates of Its Resource Needs. GAO–09–581. Washington, DC: June 19, 2009.

High-Risk Series: An Update. GAO–09–271. Washington, DC: January 2009.

Drug Safety: Better Data Management and More Inspections Are Needed to Strengthen FDA's Foreign Drug Inspection Program. GAO–08–970. Washington, DC: September 22, 2008.

[29] In our 2010 report, we noted that FDA had taken action against two of the establishments that appeared not to exist by deactivating their registration and alerting FDA import staff so that they could detain any products offered for import by these establishments, thus preventing these products from being imported into the United States.

Medical Devices: FDA Faces Challenges in Conducting Inspections of Foreign Manufacturing Establishments. GAO–08–780T. Washington, DC: May 14, 2008.

Drug Safety: Preliminary Findings Suggest Recent FDA Initiatives Have Potential, but Do Not Fully Address Weaknesses in Its Foreign Drug Inspection Program. GAO–08–701T. Washington, DC: April 22, 2008.

Medical Devices: Challenges for FDA in Conducting Manufacturer Inspections. GAO–08–428T. Washington, DC: January 29, 2008.

Drug Safety: Preliminary Findings Suggest Weaknesses in FDA's Program for Inspecting Foreign Drug Manufacturers. GAO–08–224T. Washington, DC: November 1, 2007.

Food and Drug Administration: Improvements Needed in the Foreign Drug Inspection Program. GAO/HEHS–98–21. Washington, DC: March 17, 1998.

The CHAIRMAN. Thank you very much, Dr. Crosse.

Dr. Martello, welcome and please proceed.

STATEMENT OF KENDRA A. MARTELLO, J.D., ASSISTANT GENERAL COUNSEL, PhRMA, WASHINGTON, DC

Ms. MARTELLO. Thank you very much. Mr. Chair, Ranking Member, and members of the committee, my name is Kendra Martello, Assistant General Counsel at the Pharmaceutical Research and Manufacturers of America, or PhRMA. Our members represent America's leading biopharmaceutical research companies.

Last year, industry-wide research investment was greater than $67 billion, a record. Our companies invest on average more than a billion dollars over 10 to 15 years to research and develop a new medicine. Additionally, our companies provide, directly and indirectly, millions of stable, high-paying jobs for American workers, jobs that can help fuel our Nation's economic recovery.

I'm pleased to offer this testimony today on securing the pharmaceutical supply chain. We appreciate the committee's longstanding interest in this issue and want to acknowledge, in particular, the commitment of the Chairman, Ranking Member, and Senator Bennet to considering solutions to these important issues.

My remarks today will focus on four key points. First, patient safety is of primary importance. Patients trust that the medicines they take meet high standards set by the Food and Drug Administration, no matter where they're made. And PhRMA member companies are committed to improving the lives of patients and to producing high-quality, safe, and effective drug products.

Second, the U.S. drug review, approval, and oversight system is the gold standard worldwide. It's this comprehensive regulatory system coupled with our closed distribution system—closed by Congress in the mid-1980s—that helps provide the high level of product quality, safety, and integrity that we enjoy today. No one aspect of the system in isolation is responsible for protecting our secure supply chain.

In addition to the requirement to obtain approval of a new drug application before a new drug can be sold, manufacturers must also follow current good manufacturing practices. These regulations recognize that testing and inspections alone cannot ensure the quality of a product. These NDA and GMP requirements apply to all new drugs sold in the United States, no matter where they're made, and GMPs apply to all components of the finished drug, including active pharmaceutical ingredients, no matter where they're sourced.

Third, supply chain security is a shared responsibility. Even with our comprehensive regulatory system, the globalization of pharma-

ceutical supply chains presents new challenges that require us to be adaptive and flexible. Everybody has a role to play. Every manufacturer, whether brand or generic, OTC, or component—recognizing that nearly 80 percent of the drugs dispensed in the United States are for generic medicines—and every importer and distributor has a role to play in the safety and the security of the drug supply chain.

We all must work together, and PhRMA and its member companies are committed to doing our part. To the extent that an entity, whether a finished product or a bulk ingredient manufacturer or another entity in the supply chain, circumvents established requirements, they place patients at risk and disadvantage those who strive to comply.

Fourth, as we consider challenges presented by globalization, we believe any new authorities must be grounded in sound science and driven by risk. Risk-based approaches to regulation are not new and, in fact, are widely accepted by both industry and FDA. For example, we support giving FDA the flexibility to prioritize inspections based on risk. Reliance on certain risk factors such as compliance history and time since last inspection will enable the agency to efficiently and effectively target its resources to the benefit of patients.

We also encourage giving FDA the discretion to rely on satisfactory inspection results from foreign countries with comparable drug regulatory systems or to use accredited third parties to conduct some inspections. This would in no way take the place of FDA inspections. Rather, it would allow the agency the flexibility to leverage the work of other competent authorities and maximize its own resources, all without limiting in any way its ability to inspect a particular facility.

We also believe that those who produce components and products destined for sale in the United States should register with FDA. This will help provide transparency to those who supply products and components sold here and will help FDA develop a risk-based inspection approach.

In conclusion, our comprehensive regulatory and closed distribution system helps provide assurances in the safety, quality, and integrity of the new drug products sold here in the United States. Patients rely on this system to safeguard the medicines they need to improve their health and sustain their lives.

The challenges of globalization present new opportunities to discuss how best to strengthen our existing supply chain. But they also remind us how critically important it is to maintain this existing closed distribution system. PhRMA member companies are committed to doing our part and to working with the committee, Members of Congress, and other stakeholders on this important issue.

Thank you.

[The prepared statement of Dr. Martello follows:]

PREPARED STATEMENT OF KENDRA A. MARTELLO, J.D.

SUMMARY

PhRMA represents the country's leading research-based pharmaceutical and biotechnology companies that are devoted to inventing new, life-saving medicines that help patients live longer, healthier, and more productive lives.

The regulatory system that governs the development, approval, marketing, and surveillance of new drugs and biologics in the United States is the most complex and comprehensive in the world. In addition to the requirement to obtain FDA approval of a New Drug Application (NDA) before a new drug may be sold in the United States, manufacturers of pharmaceuticals sold legally in the United States must also comply with the "gold standard" of quality manufacturing—FDA's current Good Manufacturing Practice (cGMP) regulations. These regulations apply to all new prescription drugs approved for sale in the United States, *wherever they are made* and extend to all components of a finished drug product, including active pharmaceutical ingredients (APIs), *without regard to where those ingredients are sourced.* In addition, America's prescription drug distribution system is a closed system. Coupled with the comprehensive regulatory requirements and oversight of the FDA, our closed distribution system provides assurance regarding the quality, safety and integrity of the products lawfully sold in the United States, and helps minimize the possibility of a consumer receiving a counterfeit drug.

As the committee considers the issue of securing the pharmaceutical supply chain, we are pleased to provide the following preliminary comments, and look forward to an ongoing dialogue on these important issues.

PhRMA believes that all foreign establishments manufacturing prescription drug products or components destined for import into the United States must register with FDA and list their products, to the extent they are not already required to do so under current law.

PhRMA supports granting FDA discretion to set routine inspection intervals for foreign and domestic facilities according to risk. This will enhance the FDA's ability to target its inspection resources efficiently and effectively.

Congress should consider allowing FDA to rely on the inspection results of other foreign regulatory bodies with similarly robust drug regulatory oversight systems or to use accredited third parties to conduct some foreign inspections (such as inspections of facilities considered moderate to low risk, based on appropriate criteria). This will provide FDA with the flexibility to leverage the work of foreign regulatory bodies and maximize its resources, all without foreclosing its ability to inspect any facility.

As we consider whether new authorities are needed to help strengthen our existing prescription drug supply chain, we must also consider the appropriateness of including new burdens on the import of materials for use in preclinical and clinical investigations.

Mr. Chairman, Ranking Member and distinguished members of the committee, I am pleased to testify today on the issue of "Securing the Pharmaceutical Supply Chain." My name is Kendra Martello, Assistant General Counsel at the Pharmaceutical Research and Manufacturers of America (PhRMA). PhRMA represents the country's leading research-based pharmaceutical and biotechnology companies that are devoted to inventing new, life-saving medicines that help patients live longer, healthier, and more productive lives. In 2010, America's biopharmaceutical research companies invested more than $67 billion in the research and development of new medicines.

Biopharmaceutical research and development is a complex, risky and uncertain undertaking. On average, the time to develop a new medicine is 10–15 years, at a cost of over $1.2 billion. Moreover, our companies provide—directly and indirectly—millions of stable, high-paying jobs for American workers. These jobs can help fuel our Nation's economic recovery. Accordingly, FDA's regulation of new medicines should not stifle innovation in the biopharmaceutical sector.

I. FDA OVERSIGHT OF PRESCRIPTION DRUG MANUFACTURING

America's patients trust that the medicines they take meet the high standards set by the Food and Drug Administration (FDA) for safety and efficacy and are not substandard or counterfeit, and they rely on our comprehensive drug regulatory system to help ensure that is the case. America's research-based biopharmaceutical companies also depend on a safe, secure prescription drug supply chain.

The regulatory system that governs the development, approval, marketing, and surveillance of new drugs and biologics in the United States is the most complex and comprehensive in the world. FDA regulates virtually every stage in the life of a prescription medicine sold in the United States, from pre-clinical testing of investigational compounds in animals and human clinical trials before a medicine is sold, to manufacturing, labeling, packaging, and advertising, to monitoring actual experience with the drug after its approval. Further, FDA receives information about shipments of imported goods into the United States, and has developed a risk-based information system to help facilitate the targeting of certain shipments for further examination at U.S. ports of entry.[1]

In addition to the requirement to obtain FDA approval of a New Drug Application (NDA) or a Biologics License Application (BLA) before a new drug may be sold in the United States, manufacturers of pharmaceuticals sold legally in the United States must also comply with the "gold standard" of quality manufacturing—FDA's current Good Manufacturing Practice (cGMP) regulations.[2] These regulations apply to all new prescription drugs approved for sale in the United States, *wherever they are made*, and extend to all components of a finished drug product, including active pharmaceutical ingredients (APIs), *without regard to where those ingredients are sourced*. FDA's cGMP regulations are based on the fundamental quality assurance principle that quality, safety and effectiveness "cannot be inspected or tested into a finished product," but instead must be designed and built into a product.[3] It is well-established that inspections alone cannot be relied upon to ensure product quality and integrity, but that quality systems are also vital to ensuring the product meets established specifications and requirements.[4] The quality systems approach to manufacturing drug products is embodied in the cGMP regulations.

Thus, while FDA inspections are an important part of FDA's regulatory authority and oversight, and PhRMA member companies are routinely inspected, the cGMPs represent a comprehensive, systems-based approach requiring a company to build quality directly into the entire manufacturing operation, in order to ensure that the process itself is under control and therefore will consistently produce a drug product that meets designated specifications. Further, the word "current" in front of the phrase "good manufacturing practice" in the FDCA recognizes and appreciates that these manufacturing standards are and must be flexible and adaptive to accommodate different types of products and advances in science and manufacturing technologies.

Currently, in addition to the requirement that API must be manufactured in accordance with cGMPs, manufacturers are also required to ensure that representative samples of each shipment of each lot of a drug component are tested or examined "for conformity with all appropriate written specifications for purity, strength, and quality."[5] Any lot that does not meet such specifications must be rejected by the manufacturer and may not be used.[6]

Finally, the Prescription Drug Marketing Act of 1987 (PDMA) is a critical piece of consumer legislation passed as a result of congressional investigations into the integrity of the drug distribution system that existed at the time. The PDMA created the closed prescription drug distribution system in place today, meaning that products that have circulated overseas may not lawfully be sold in the United States, unless they have remained under the control of the original manufacturer. Coupled with the comprehensive regulatory requirements and oversight of the FDA, our closed distribution system provides assurance regarding the quality, safety and integrity of the products lawfully sold in the United States, and helps minimize the possibility of a consumer receiving a counterfeit drug.

II. PRELIMINARY IDEAS TO STRENGTHEN SUPPLY CHAIN INTEGRITY

Even with FDA's comprehensive regulatory system, increasing globalization of pharmaceutical supply chains presents challenges that require biopharmaceutical

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[1] See Statement of Margaret A. Hamburg, M.D., Commissioner of Food and Drugs, Before the Subcommittee on Oversight & Investigations, Committee on Energy & Commerce, "Import Safety: Status of FDA's Screening Efforts at the Border," April 13, 2011.

[2] Under current law, a drug is adulterated if the methods used in, or the facilities or controls used for, manufacturing a drug product do not conform to cGMPs, and FDA regulations and guidance provide additional clarification regarding the expectations of cGMPs in drug product manufacturing. 21 U.S.C. § 351(a)(2)(B).

[3] 61 Fed. Reg. 20104, 20105 (May 3, 1996).

[4] See generally 21 CFR Parts 210 and 211.

[5] 21 CFR § 211.84(d)(2).

[6] 21 CFR § 211.84(e).

companies and the FDA to be more adaptive and flexible in the review and oversight of entities located around the world.

FDA should use its powerful existing enforcement authorities to take action against violative products and to promote accountability among regulated entities—enforcement authority that the FDA under the current Administration has made a priority to exercise when warranted. In short, supply chain security is the responsibility of all parties involved in the distribution of medicines to American patients. We appreciate the committee's long-standing commitment to these issues. As the committee considers the issue of securing the pharmaceutical supply chain, we are pleased to provide the following preliminary comments, and look forward to an ongoing dialogue on these important issues.

A. Registration of Foreign Facilities

PhRMA believes that all foreign establishments manufacturing prescription drug products or components destined for import into the United States must register with FDA and list their products, to the extent they are not already required to do so under current law. By requiring such facilities to register, the FDA will be able to establish a single database that will contain information on all facilities that manufacture products or components of products that are sold in the U.S. Prior Congressional testimony and Government Accountability Office reports suggest that such information appears in several different formats and databases managed by FDA, and, therefore, it is not easily accessible or usable by Agency personnel. A single, standardized database would, among other things, allow the FDA to help ensure that all facilities subject to inspection are identified, that FDA inspections can be prioritized, and that routine inspections occur at appropriate intervals. FDA Commissioner Hamburg has also expressed support for modernizing the Agency's registration and listing function.[7]

B. Enhancements to FDA's Inspection Regime

i. Risk-Based Inspection Intervals

PhRMA supports granting FDA discretion to set routine inspection intervals for foreign and domestic facilities according to risk. The use of risk-based approaches to regulation, and in particular, to cGMP inspections is not a new concept.[8] We support providing FDA with the flexibility to prioritize inspections of foreign establishments based on the risks they present, and believe relying on set criteria such as compliance history, time since last inspection, and volume and type of products produced, will enhance the FDA's ability to target its inspection resources efficiently and effectively.

ii. Increase Foreign cGMP Inspections

We also recognize that while FDA has broad authority to conduct inspections of domestic and foreign facilities, it currently conducts limited numbers of cGMP inspections of foreign facilities, including API manufacturers. Therefore, we recommend that FDA generally increase its cGMP inspections of foreign facilities, including API manufacturers, to help ensure that cGMPs are being followed. The targeting of these increased foreign inspections should be accomplished by utilizing the risk-based approach described above.

iii. Foreign Inspection Reports/Accredited Third Parties

In recognition of the fact that the Agency does not have unlimited resources and in order to help ensure that foreign inspections occur on a more regular basis, Congress should consider allowing FDA to rely on the inspection results of other foreign regulatory bodies with similarly robust drug regulatory oversight systems or to use accredited third parties to conduct some foreign inspections (such as inspections of facilities considered moderate to low risk, based on appropriate criteria). These inspections would not take the place of FDA inspections, which are a necessary and important part of the Agency's mandate; however, they would provide FDA with the flexibility to leverage the work of foreign regulatory bodies and maximize its resources, all without foreclosing its ability to inspect any facility. FDA recently acknowledged and embraced the concept of relying on "public and private third parties

[7] See Statement of Margaret A. Hamburg, M.D., Commissioner of Food and Drugs, Before the Subcommittee on Oversight & Investigations, Committee on Energy & Commerce, "Import Safety: Status of FDA's Screening Efforts at the Border," April 13, 2011.

[8] See e.g., "FDA Guidance: Risk-Based Method for Prioritizing GMP Inspections of Pharmaceutical Manufacturing Sites—A Pilot Risk Ranking Model," (Sept. 2004).

to conduct audits and other oversight activities on behalf of FDA."[9] FDA intends to quickly "establish the framework and approach for capturing this opportunity."[10]

iv. Exemption for Materials Intended for Research Use

As we consider whether new authorities are needed to help strengthen our existing prescription drug supply chain, we must also consider the appropriateness of including new burdens on the import of materials for use in preclinical and clinical investigations. The continued, uninterrupted access to clinical trial materials, including APIs, is essential to ensure that vital research into innovative, life-saving and life-enhancing new treatments is not hindered in any way. Materials and articles used in pre-clinical research and development activities are never consumed by humans, but instead are used in laboratory testing as scientists try to understand how the test article works and its safety profile. The FDA requires reports of non-clinical laboratory testing and the submission of detailed information in a range of areas in order to justify the study of a candidate drug in humans, and materials used in the pre-clinical research and development process are not studied in humans. Further, investigational drugs and drug components imported for use under an Investigational New Drug (IND) application are subject to strict FDA regulation and oversight at all times and must be manufactured according to cGMPs, including appropriate standards for testing and quality control.

Thus, we strongly encourage the inclusion of an exemption for drugs, API, and other materials intended for use in clinical trials that comply with other FDA requirements relating to the proper use of investigational material, including labeling and import of investigational products and materials for use in U.S.-based clinical trials under an IND application filed with the FDA into any new provisions related to securing our pharmaceutical supply chain. Including these investigational products and materials in any new provisions could potentially be duplicative of existing requirements. Additionally, exempting investigational materials, drugs, and drug components used for pre-clinical and clinical research from any new provision could help ensure that the development of new medicines is not delayed or hindered and that clinical trials and research and development continue to occur in the United States—thus helping ensure that related jobs stay in the United States as well.

III. CONCLUSION

We commend the committee for its focus on and commitment to the issue of securing the pharmaceutical supply chain. We recognize the importance of ensuring that the regulatory system in place today for prescription drugs continues to remain the best and the safest in the world. We cannot underemphasize the potential that exists for unsafe and potentially dangerous counterfeit drugs to enter the United States should Congress act to open our borders to more expansive prescription drug importation proposals. These proposals would allow non-U.S.-approved drug products to be sold on U.S. pharmacy shelves next to FDA-approved drug products that have undergone our rigorous testing, review and approval process and put American patients at risk, and the FDA agrees.[11]

Our system of prescription drug supply chain security today is very, very good, but even good systems can be improved upon. We look forward to continuing to work with the committee, FDA, and other stakeholders on these important issues. Thank you for the opportunity to testify today and I welcome any questions you may have.

The CHAIRMAN. Thank you very much, Dr. Martello.

And now we'll turn to Mr. Gordon Johnston with the Generic Pharmaceutical Association.

Welcome and please proceed, Mr. Johnston.

STATEMENT OF GORDON JOHNSTON, SENIOR ADVISOR FOR REGULATORY SCIENCES, GPhA, WASHINGTON, DC

Mr. JOHNSTON. Good morning, Chairman Harkin, Ranking Member Enzi, and members of the committee. Thank you for asking me

[9] "Pathway to Global Product Safety and Quality: Special Report," Food and Drug Administration, (July 7, 2011), at 31, available at: *<http://www.fda.gov/AboutFDA/CentersOffices/OC/GlobalProductPathway/default.htm>*.

[10] *Id.*

[11] See e.g. FDA Home Page: "Importing Prescription Drugs," *<http://www.fda.gov/Drugs/DrugSafety/ucm170594.htm.>*.

to participate in this timely and important hearing. I am Gordon Johnston, senior advisor for regulatory sciences at the Generic Pharmaceutical Association, or GPhA.

GPhA represents the manufacturers and distributors of generic pharmaceuticals and active ingredients. Generic pharmaceuticals now fill 78 percent of all prescriptions dispensed in the United States but consume just 25 percent of the Nation's total drug expenditure.

Prior to joining GPhA, I served in the U.S. Public Health Service and in 1987 was assigned to the Food and Drug Administration and became the Deputy Director of the Office of Generic Drugs in 1994.

Securing the Nation's pharmaceutical supply chain is of vital importance to GPhA and our member companies. We also have a keen interest in a level, competitive, and accountable playing field among all participants in the U.S. pharmaceutical supply chain. We commend the committee for your focus on ensuring the safety of America's pharmaceutical supply, brand and generic.

GPhA is committed to doing everything possible to work with Congress and the FDA to promote a vigorous and rigorous oversight of the Nation's drug supply. As the committee begins to take a closer look at this important issue, it's critical to understand the fundamental underpinnings of the current system and acknowledge the global dynamics of our pharmaceutical supply here in the United States.

First, as my colleague at PhRMA mentioned, I certainly want to make it clear that the U.S. drug supply is the safest in the world. However, we recognize that globalization has added new and complex challenges to continue to assure this safety.

The pharmaceutical marketplace that FDA oversees in today's global age, however, looks drastically different than it did in 1938 when Congress passed the statute, and that's the Federal Food, Drug, and Cosmetic Act. As mentioned previously, today, nearly 40 percent of all prescription drugs dispensed in the United States are manufactured outside of the country, and nearly 80 percent of the ingredients used in these drugs are manufactured abroad.

According to FDA estimates, the number of drug products made outside of the United States doubled between 2001 and 2008. Unfortunately, this growth has outpaced the law's reach as well as the funds needed to allow FDA to hold all participants to the same high-quality standards.

The act of 1938 requires American drug manufacturers to undergo surveillance inspections at least every 2 years to confirm that these facilities are complying with good manufacturing standards. However, the act does not impose the same biennial GMP inspection requirement on foreign facilities.

Further, this disparity in the degree of oversight experienced by domestic versus foreign facilities reduces American competitiveness by creating an uneven playing field while at the same time creates opportunity for threats to the U.S. drug supply. Also, delays in foreign inspections slow the approval of products that serve unmet medical needs such as those facing drug shortages.

To paraphrase the recent statements by HHS Secretary Kathleen Sebelius and FDA, HHS and FDA are looking to Congress to mod-

ernize its antiquated authorities so that FDA's legal tools can keep pace with globalization. GPhA is in agreement with the Secretary and FDA that it's essential to modernize the laws governing the U.S. supply chain.

As noted in my opening remarks, the responsibility of ensuring safety is a shared one that rests with all of us in industry and not just FDA. As my colleagues at Pew noted in their recent report, it's also critical that manufacturers continue to go beyond GMPs and assure that their supplier qualification tools are used, using risk-based assessment to assure the quality and integrity of suppliers abroad. Such practices which are intended to prevent potential contamination and adulteration should also be supplemented by a Federal pedigree tracking system with uniform standards across all States as opposed to a patchwork of random State-enforced regulations.

Even with these significant efforts in place, however, the generic industry has realized that more needs to be done. That's why the industry stepped up to the plate and is now finalizing a generic drug user fee program with FDA. One of the main goals of this user fee program is to hold all generic players, foreign and domestic, to the same GMP inspection standards and enhance FDA's ability to identify, track, and register all contributors involved in the generic drugs in the United States.

In conclusion, Mr. Chairman, GPhA stands ready to support Congress and FDA in strengthening its oversight, updating the law, and investing more resources to ensure that the United States continues to be a leader in the world when it comes to safety and also maintaining the American industry's competitiveness.

I thank you for this time and would be happy to address any questions from the committee as we move forward.

[The prepared statement of Mr. Johnston follows:]

PREPARED STATEMENT OF GORDON JOHNSTON

SUMMARY

I am Gordon Johnston, Senior Advisor for Regulatory Sciences at the Generic Pharmaceutical Association, which represents the manufacturers and distributors of finished dose generic pharmaceuticals, manufacturers and distributors of bulk pharmaceutical chemicals and suppliers of other goods and services to the generic industry. Given that more than 78 percent of all prescription drugs dispensed in this country are generic drugs, GPhA has a keen interest in making sure the supply chain is safe for consumers. We also have a keen interest in a level, competitive and accountable playing field among all participants in the U.S. supply chain.

Today, nearly 40 percent of all prescription drugs dispensed in the United States are manufactured outside of the country and nearly 80 percent of the ingredients in our drugs are manufactured abroad. With a mission to protect and promote the public health, the Food and Drug Administration is charged with ensuring the safety of all medicine sold in the United States no matter where these products are made. According to FDA estimates, the number of drug products made outside of the United States doubled from 2001 to 2008.

One of the most critical ways FDA ensures continued compliance with the high quality standards required of prescription drugs sold in the United States is by conducting on-site inspections of facilities where drugs are manufactured. FDA's guiding statute, the Federal Food, Drug and Cosmetic Act of 1938 ("FDCA"), requires American manufacturers to undergo a surveillance inspection every 2 years to ensure that these facilities are complying with these high quality standards known as good manufacturing practices ("GMP"). However, the FDCA does not impose the same surveillance inspection requirement on foreign facilities. According to FDA, foreign facilities have grown by 185 percent, while at the same time FDA inspection rates have decreased by nearly 57 percent. Meanwhile, according to the Government

Accountability Office, the FDA inspected just 11 percent of the 3,765 foreign establishments in its database in 2009.

Unfortunately, this global growth has outpaced the reach of the FDCA, which was written nearly seven decades ago when the U.S. drug supply was domestic and not the global one that it is today. In the recent words of the FDA, the agency is "looking to Congress to modernize its antiquated authorities so that FDA's legal tools keep pace with globalization."

Even though these global challenges impact the entire pharmaceutical industry, brand or generic, the generic drug industry has stepped up to help provide FDA with additional resources to address the challenges caused by the global drug supply and the increase in FDA workload. The industry has been working closely with FDA to finalize negotiations on a generic drug user fee program to help the FDA obtain additional resources to ensure all participants in the U.S. generic drug system, whether U.S.-based or foreign, comply with U.S.-strict quality standards and make certain Americans get more timely access to low-cost, high-quality generic drugs. The generic drug user fee program being finalized now recognizes that while providing earlier access to effective medicines is critical (the key aim of all other existing user fee programs), an equally important pillar of FDA's mission is ensuring drug safety. In addition, it is also critical that we as manufacturers continue to go beyond current GMP standards in our own facilities to ensure appropriate supplier qualification, through risk-based assessments, quality agreements and physical audits, where appropriate. By working together as an industry to share the results of these audits, as well as new technologies, we can further develop harmonized standards and best practices to ensure that all stakeholders in the pharmaceutical supply chain are utilizing the most current and effective methods for providing patients with safe and effective medications.

While these efforts provide an excellent framework for industry to help support the growing global needs of FDA and to level the playing field between foreign and domestic facilities through inspection parity, they do not completely solve the problem. To globalize FDA's authority, eliminate the inspection disparity and better ensure the safety of the global supply chain, it is paramount that a bill is introduced to expand FDA's authorities to achieve its mission in this global age.

The safety of our Nation's pharmaceutical supply is only as good as our weakest link, and the responsibility rests on all of us. GPhA encourages Congress and our counterparts throughout the pharmaceutical industry to work together to ensure FDA is equipped to keep our consumers safe in a 21st century global drug supply environment.

Good morning Chairman Harkin, Ranking Member Enzi and members of the Senate Committee on Health, Education, Labor, and Pensions. Thank you for asking me to participate in this very timely and important hearing.

I am Gordon Johnston, Senior Advisor for Regulatory Sciences at the Generic Pharmaceutical Association. GPhA represents the manufacturers and distributors of finished dose generic pharmaceuticals, manufacturers and distributors of bulk pharmaceutical chemicals and suppliers of other goods and services to the generic industry. Generic pharmaceuticals now fill 78 percent of all prescriptions dispensed in the United States, but consume just 25 percent of the total drug spending.

According to an analysis by IMS Health, the world's leading data source for pharmaceutical sales, the use of FDA-approved generic drugs in place of their brand counterparts saved U.S. consumers, patients and the health care system more than $824 billion over the past decade—$137 billion in 2009 alone—which equates to $1 billion in savings every 3 days.

Prior to joining GPhA, I was with the U.S. Public Health Service, where I served in a number of pharmacist and health care management positions. In 1987, I was assigned to the Food and Drug Administration and, in 1994, became the Deputy Director of the FDA's Office of Generic Drugs (OGD). While at the FDA, my duties required that I interfaced with a number of foreign governments on drug safety and regulatory standards.

INTRODUCTION

I would like to make two brief points in my testimony today, before providing comments on securing the pharmaceutical supply chain.

First, we commend the committee for your focus on ensuring the safety of America's pharmaceutical supply—brand and generic. For nearly a quarter of a century America's generic drug industry has been developing, manufacturing and marketing generic versions of brand-name prescription drugs. Last year, approximately 78 per-

cent of the more than 3 billion new and renewal prescriptions dispensed in the United States were filled with generics, saving patients and consumers billions of dollars. We are committed to doing everything possible to work with Congress and the FDA to ensure that adequate oversight of the Nation's drug supply is in place to ensure its safety.

Second, the generic pharmaceutical industry is among the most highly regulated in the world, with strict rules governing the development, manufacture, approval, packaging, marketing and post-marketing surveillance of prescription drugs by the FDA. These stringent regulations apply equally to all pharmaceutical products—brand or generic, approved by the FDA.

Securing the Nation's pharmaceutical supply chain is of vital importance to the Generic Pharmaceutical Association and to our member companies. Given that more than 78 percent of all prescription drugs dispensed in this country are generic drugs, we have a keen interest in making sure the supply chain is safe for American consumers who rely on our medicines. We also have a keen interest in a level, competitive and accountable playing field among all participants in the U.S. pharmaceutical supply chain.

CURRENT LANDSCAPE

As the committee begins to look closer at this important issue, it is critical to understand the fundamental underpinnings of the current system that ensures drug safety in our country and acknowledge the global dynamics of our current branded and generic pharmaceutical supply here in the United States.

While much of the responsibility of ensuring safe drugs rests with industry, the FDA plays a critical role in making sure all players participating in the pharmaceutical supply chain meet FDA's rigorous standards, including compliance with current Good Manufacturing Practices ("GMP"). With a mission to protect and promote the public health, the FDA is charged by Congress to ensure the safety, efficacy and security of the U.S. drug supply and to address threats to public health.

BACKGROUND ON FDA'S AUTHORITY

FDA's authority to carry out this responsibility originated some seven decades ago when President Franklin Roosevelt signed into law the Federal Food, Drug and Cosmetic Act of 1938 following the death of more than 100 people as a result of ingesting Elixir Sulfanilamide, which contained the deadly poison diethylene glycol. In an effort to avoid future tragedies, this landmark legislation of 1938 became the foundation on which the FDA oversees our Nation's pharmaceutical supply today. Among other authorities, this law authorized FDA to demand evidence of safety and conduct facility inspections, two critical authorities of the world's most robust drug authority.

THE PROBLEM

The pharmaceutical marketplace FDA oversees in today's global age, however, looks drastically different than it did in 1938 when FDA's guiding statute was enacted. And several unfortunate tragedies in the pharmaceutical world since 1938 have prompted further enhancements to FDA's authority under the FDCA to ensure the agency is equipped to carry out its mission of protecting the public health. A few pivotal events have led to an enhancement of FDA's original 1938 authority since the law's original passage. This included the thalidomide tragedy in Europe, which strengthened the rules for drug safety and required manufacturers to prove their drugs' effectiveness in the United States in 1962. In 1976, additional amendments were made to apply safety and effectiveness safeguards to new devices following a U.S. Senate finding that faulty medical devices had caused 10,000 injuries, including 731 fatalities.

Unfortunately, as this committee is aware, the United States experienced another tragedy recently when tainted brand Heparin was distributed in the United States, leading to 81 deaths and shedding additional light on some notable shortcomings of the 1938 law, which makes it more difficult for FDA to carry out its mission in the now very globalized U.S. pharmaceutical supply chain. FDA traced the adulteration of the Heparin product to a manufacturing facility in China, which the agency had never inspected. As globalization of drug supply increases, so do concerns about drug safety and demands to preserve the stringent quality standards Americans deserve, regardless of where their medicines are produced.

Today, nearly 40 percent of all prescription drugs dispensed in the United States are manufactured outside of the country, and nearly 80 percent of the ingredients in our drugs are manufactured abroad. The Food and Drug Administration is charged with ensuring the safety of all medicine sold in the United States no matter

where these products are made. According to FDA estimates, the number of drug products made outside of the United States doubled from 2001 to 2008. The growth in the number of facilities requiring FDA oversight has grown substantially, particularly in foreign facilities that supply the U.S. marketplace. In 2010, nearly 20 million shipments of food, drugs and cosmetics arrived at U.S. ports of entry. A decade earlier, that number was closer to 6 million and, a decade before, just a fraction of that figure. Unfortunately, this growth has outpaced the law's reach as well as the funds needed to allow FDA to hold all participants in the pharmaceutical supply chain to the same high quality standards.

MORE FOREIGN INSPECTIONS NEEDED

One of the most critical ways FDA ensures continued compliance with the high quality standards required of prescription drugs sold in the United States is conducting on-site inspections of facilities where drugs are manufactured. These important surveillance inspections ensure that facilities are continuing to meet their obligation of producing safe products in accordance with a rigorous set of standards known as Good Manufacturing Practices, or GMP, and serve as a critical tool of ensuring continued safety and GMP compliance—separate and distinct from other supply chain controls.

The FDCA of 1938 requires American manufacturers associated with pharmaceutical production to undergo a surveillance inspection every 2 years to ensure that these facilities are complying with strict GMP standards. However, the FDCA does not impose the same biennial GMP inspection requirement on foreign facilities. According to FDA, foreign facilities have grown by 185 percent, while at the same time FDA inspection rates have decreased by nearly 57 percent. Meanwhile, the FDA inspected just 11 percent of the 3,765 foreign establishments in its database in 2009, according to the Government Accountability Office.

This disparity in the degree of oversight experienced by domestic versus foreign facilities reduces American competitiveness by creating an uneven playing field, while at the same time threatening the safety of the U.S. drug supply.

This disparity in inspections between foreign and domestic facilities is also causing notable delays in introducing new prescription drugs to consumers, including delays in approving products that serve an unmet medical need or offer a more affordable alternative in the case of generic drugs. This is because new product approvals, such as those facing drug shortages, require an inspection history of the relevant manufacturing facility and, given the number of facilities awaiting inspection, many of the facilities producing new drugs are waiting to be inspected.

THE SOLUTION

FDA does indeed need, in the words of Health and Human Services Secretary Kathleen Sebelius, "additional tools from Congress to move its oversight capabilities into the 21st century." And more recently, the agency noted that it is "looking to Congress to modernize its antiquated authorities so that FDA's legal tools keep pace with globalization."

GPhA is in agreement with FDA on this matter. Without modernization of the law governing the U.S. drug supply and increased authority and resources to carry out FDA's oversight of today's complex and global drug supply, the significant challenges facing the U.S. pharmaceutical marketplace will continue and likely compound. Earlier this year, the President signed into law legislation intended to globalize FDA to help protect the Nation's food supply and equip the agency to carry out its twin mission of ensuring food safety in an increasingly globalized food supply. When it comes to drugs, however, FDA still operates in accordance with the FDCA of 1938, the scope and provisions of which are largely domestic. This law needs to be globalized to ensure FDA is equipped for the global age and to ensure competitiveness.

GPhA is pleased the committee is holding this hearing to begin efforts to equip FDA with the necessary legal authority and tools to carry out its critical public health mission in the globalized U.S. pharmaceutical marketplace.

Ensuring that all contributors to the U.S. drug system, both foreign and domestic, are held to the same quality standard is a critical issue for the entire pharmaceutical industry—brand and generic alike. Amending the FDCA of 1938 and, in particular, ensuring foreign facilities are held to the same standards as U.S. facilities, will improve quality, consistency and availability within the drug supply chain and create a level playing field, allowing U.S. pharmaceutical manufacturers to be more competitive. These important updates to the law will not only result in a safer drug supply with consistent oversight for all players in the U.S. system, the changes

will also help reduce approval times of new drugs undergoing FDA review and help expedite the availability of new medicine.

GPhA further supports a "risk-based" model for inspections that prioritizes inspections according to a company's safety and compliance track record. This system would ensure that questionable or problematic facilities receive a comprehensive review and evaluation sooner, rather than later, or not at all as is the case under the current system. Facilities with strong records of compliance and positive inspections would be placed further down on the inspection schedule, allowing the agency to prioritize its immediate attention on companies that have never had an inspection or that have a history of compliance issues.

GENERIC DRUG INDUSTRY STEPS UP TO HELP ADDRESS THIS INDUSTRY-WIDE ISSUE

As I noted in my opening remarks, the responsibility of ensuring safety is a shared one that rests with all of us in industry, though, not just the FDA.

I am proud to say that the generic drug industry has been a leader in this area, developing supply-chain security measures independently and with the FDA to provide the necessary oversight to maintain the Nation's drug supply.

For example, one new initiative is the FDA's border control policy, which is being developed in an attempt to cut the number of poor standard medicines that enter the supply chain from outside the United States. The new initiative, which is called PREDICT—Predictive Risk-based Evaluation for Dynamic Import Compliance Targeting—will be a border-based scheme that assesses drugs at the point of import. Barcodes on cases of medicines will be scanned at the U.S. borders and linked to a central database. The results will be able to tell the FDA agents at the border whether or not the producer has a license to ship and sell their drugs in the United States. If the products do not meet FDA compliance they will not be allowed into the country.

The pharmaceutical industry also provides multiple layers of testing and oversight to build in quality and supply chain security from the ground up. Suppliers of inactive and active ingredients are carefully evaluated to assess their facilities, manufacturing capabilities and supply chain practices and controls. These initiatives provide the foundation of drug product quality, as well as taking all necessary steps to help eliminate potential contamination or adulteration in the shipment channels. Next, manufacturers test the incoming raw materials for quality, purity and potency in accordance with FDA-approved analytical methods. These testing methods are designed to assure that all raw materials meet their predetermined quality attributes. Finished dosage form manufacturers have sophisticated testing procedures during the manufacturing process and for the final product, which are all intended to assure that the product received by patients meets all standards for quality, purity and potency.

As drug products are shipped to wholesalers, pharmacies or other intermediaries, the pharmaceutical industry utilizes multiple forms of controls within the supply chain to mitigate the potential risk of contamination or adulteration. Careful planning of drug shipments, along with strict supply chain custody and controls, are part of the advanced logistical operations that provide accountability and oversight of the products before they ever reach a patient's hands. By following these standards, manufacturers are able to determine any deviation from a product's predetermined shipment and custody program, and stop problems before they occur.

As my colleagues at Pew noted in their recent report, it is also critical that we as manufacturers continue to go beyond current GMP standards in our own facilities to ensure appropriate supplier qualification, through risk-based assessments, quality agreements and physical audits, where appropriate. By working together as an industry to share the results of these audits, as well as new technologies, we can further develop harmonized standards and best practices to ensure that all stakeholders in the pharmaceutical supply chain are utilizing the most current and effective methods for providing patients with safe and effective medications.

LANDMARK USER FEE PROGRAM WILL PROVIDE ADDITIONAL RESOURCES

Even with these significant efforts in place, however, the generic pharmaceutical industry has realized that more needs to be done. That is why the industry, which accounts for 78 percent of all prescription drugs dispensed in the United States, has stepped up to the plate to help provide FDA with resources to address the challenges caused by the global drug supply and the increase in the FDA's workload. The industry has been working closely with FDA to negotiate a generic drug user fee program to help the agency obtain additional resources in this global age to ensure all participants in the U.S.-generic drug system, whether U.S.-based or foreign,

comply with all U.S.-strict quality standards and to make certain Americans get timely access to low-cost, high-quality generic drugs.

The generic drug user fee program being finalized now with FDA recognizes that while providing earlier access to effective medicines is critical—and the key aim of all other existing user fee programs—an equally important pillar of FDA's mission is ensuring drug safety. The overall goal is to hold all players, foreign or domestic, contributing to the U.S. generic drug system to the same GMP inspection standards, while expediting access to more affordable, high-quality generic drugs; and, enhancing FDA's ability to identify, track and require the registration of all contributors involved in each generic drug product sold in the United States. Final recommendations are expected to be submitted to Congress in January 2012.

While the generic drug user fee program provides an excellent framework for industry to help support the growing global needs of FDA and to level the playing field between foreign and domestic facilities through inspection parity, it does not completely solve the problem, nor does it have the reach of the entire pharmaceutical industry. To globalize FDA's authority, eliminate the inspection disparity and better ensure the safety of the global supply chain, it is paramount that a bill is introduced to expand FDA's authorities to achieve its mission in this global age.

The safety of our Nation's pharmaceutical supply is only as good as our weakest link, and the responsibility rests upon all of us. GPhA encourages Congress and our counterparts throughout the pharmaceutical industry to work together to ensure FDA is equipped to keep our consumers safe in a 21st century global drug supply environment.

FEDERAL PEDIGREE STANDARD SHOULD REPLACE STATE-BY-STATE PATCHWORK

Finally, as we look at the broader issue, GPhA also recommends that Congress adopt a Federal pedigree system with uniform standards across all States, as opposed to a patchwork of more state-enforced regulations that are starting to arise in the absence of Federal leadership mandating one uniform standard. Given that products are distributed throughout interstate commerce and across all States lines, having what could potentially be a 50-state patchwork of different standards will be a mess without a Federal mandate setting a reasonable, uniform standard. The challenge to implementation will be to ensure that the technology is reasonable and feasible in light of numerous economic, technical and logistical factors so that the end product does not result in an increase to consumer and payer cost.

CONCLUSION

In conclusion, Mr. Chairman, the Generic Pharmaceutical Association stands ready to support Congress and the FDA in strengthening its oversight, updating the law and investing more resources to ensure we continue to lead the world in safety while maintaining competitiveness.

Thank you. I would be happy to address any questions of the committee.

The CHAIRMAN. Thank you very much, Mr. Johnston.

Now we'll turn to Mr. VanTrieste.

Welcome and please proceed, Mr. VanTrieste.

STATEMENT OF MARTIN VAN TRIESTE, R.Ph., PAST CHAIR, RX-360, THOUSAND OAKS, CA

Mr. VANTRIESTE. Chairman Harkin, Ranking Member Enzi, and members of the committee, thank you for the opportunity to testify today. My name is Martin VanTrieste, and I am the senior vice president of Quality at Amgen, a leading biotechnology company. In addition, I am the founder, past chair, and director of Rx-360, and it's on behalf of Rx-360 that I testify here today.

Rx-360 was founded in 2009 in direct response to the economically motivated adulteration of Heparin with the mission to enhance the security and quality of the pharmaceutical supply chain. Our membership has quickly grown to over 65 member companies, including most of the large pharmaceuticals, biotechnology, and generic drug manufacturers, along with our key suppliers.

This industry is extensively regulated by the FDA in a variety of ways, including through compliance with good manufacturing

practices, or GMPs. However, economically motivated adulteration and counterfeiting are not GMP issues. GMPs keep honest people honest but do little to prevent unethical players or criminals to exploit the complexities of the supply chain.

Let me give you an example where a lack of transparency in the supply chain was able to be exploited which is outlined in a chart I have submitted to the committee and is up here on the easel. Glycerin is an inactive ingredient used in many pharmaceuticals. In this case, the government of Panama unknowingly purchased adulterated glycerin to be used in cough syrup which resulted in at least 67 deaths.

An investigation into this tragedy revealed several breakdowns in the supply chain which were hidden from the manufacturer purchasing the ingredient. As illustrated in Box 1, the problem began in China at the Taixing Glycerin Factory which produced a technical substitute for glycerin which was not pure glycerin at all but actually contained antifreeze which is three times cheaper than glycerin.

This factory was never inspected by the Chinese FDI, and as Boxes 2, 3, and 4 describe, a series of brokers and traders moved the material through the supply chain, changing the name of the material, the manufacturing site, the expiration date of the product, and never performed any tests. This adulterated glycerin was then used to manufacture cough medicine, leading to fatal consequences.

Learning from this example, if the manufacturer of the cough syrup knew that they were really purchasing antifreeze, these fatalities would have been prevented. And this is why transparency of the supply chain is so important.

Rx-360 members recognize that we are responsible for our suppliers and the supply chains and must address the challenges associated with the global supply chain. In our short period of existence, we have implemented many solutions in four key areas. These include conducting and sharing of detailed audits of our suppliers, developing technologies to prevent and detect adulterations, implementing best practices for industry, and conducting active surveillance and issuing supply chain securities for our members.

All these efforts are intended to be key pieces of a proactive attempt to eliminate security gaps in the supply chain. The FDA is full of good people doing a tough job, and we intend these activities to be complementary of their extensive work in this area.

As policymakers look at ways to improve the integrity of the supply chain, it is important that any legislative or regulatory proposals are carefully considered, such as adding to the complexity of the supply chain, creating unintended drug shortages, and adding significant costs to the healthcare system. As you examine these issues, I have a few points for consideration.

First, some issues are related to the fact that ingredient suppliers don't always disclose the actual manufacturing site of those ingredients to drug manufacturers. This was the issue in the glycerin example I discussed earlier. By requiring a disclosure to the drug manufacturer, we can ensure enhanced oversight of our suppliers.

Second, there are many foreign suppliers who register with the FDA but have no intention of distributing product within the United States. They use this registration to convey some sense of FDA approval and undermining the integrity of the registration system.

Other points that are worth considering include increased FDA inspections of foreign manufacturers, using investigators who are specifically trained in fraud detection, allowing the use of qualified third-party inspectors, and increased criminal penalties for knowingly engaging in economic adulteration and counterfeiting.

In conclusion, on behalf of Rx-360, I thank the committee for its examination of this issue. I appreciate Senator Bennet's work in this area and the interest of Chairman Harkin and Ranking Member Enzi in finding solutions to these complex issues. Rx-360 stands ready to assist the committee as they continue to work on this important issue.

Thank you.

[The prepared statement of Mr. VanTrieste follows:]

PREPARED STATEMENT OF MARTIN VANTRIESTE, R.PH.

SUMMARY

Management of the biopharmaceutical supply chain has become one of the top public health concerns with respect to consumer safety. The globalization of distribution for drug raw materials, components and finished products has introduced many complications. This has resulted in unethical players along the supply chain introducing counterfeited, adulterated and contaminated materials, often with tragic consequences.

The biopharmaceutical industry is extensively regulated by the FDA in a variety of ways, including through compliance with Good Manufacturing Practices (cGMP). However, economically motivated adulteration and counterfeiting are not a GMP compliance issue. GMP's keep the honest people honest but do little to prevent unethical players or criminals from exploiting the supply chain.

Given these challenges, leaders in quality from the biopharmaceutical industry came together to proactively find solutions. The result was the formation of a consortium called Rx-360 in June 2009. The purpose of Rx-360 is to enhance the security of the pharmaceutical supply chain by (1) Adopting standards and best practices; (2) Developing and implementing technology (3) Conducting surveillance; and (4) Sharing supplier audit information.

Rx-360 has accomplished much in its short period of existence. It recently announced positive results from an audit pilot program which allowed audits of a supplier to be shared with the Rx-360 membership. In effect, this method reduces the number of audits that a supplier must host and that a biopharmaceutical firm must conduct themselves, all while providing more information on a particular supplier than previous audits have been able to.

Additionally, the consortium is undertaking the following activities: (1) Rx-360 has adopted, or is in the final stages of adopting, numerous standards and best practices to secure the supply chain which many firms have implemented; (2) Rx-360 has developed an analytical technique that is used by our members to detect potentially economically motivated adulteration in response to raw material shortage; and (3) Rx-360 conducts active surveillance to regularly alert its membership regarding potential supply chain issues so that companies and suppliers can implement preventative corrective measures.

Rx-360 appreciates that policymakers are examining ways to improve supply chain security, to compliment these initiatives already underway, and would like to be a resource as you examine these issues going forward. However, it is important that any legislative or regulatory proposals are carefully considered so as to ensure that there are no unintended consequences, such as adding complexity to an already complex system, unintentionally creating drug shortages, and adding significant cost to the health care system.

As you examine these issues some points for consideration which could improve supply chain security include: (1) Requiring ingredient suppliers to disclose their actual manufacturing site to manufacturers; (2) FDA registration of only those foreign

ingredient manufacturing sites whose products are used in the United States and pay a nominal fee; (3) FDA inspection of foreign ingredient manufacturing sites using a risk-based approach where the cost of the inspection is paid for by the manufacturer; and (4) Increased criminal penalties for those involved in economically motivated adulteration or counterfeiting of pharmaceuticals.

Rx-360 thanks the committee for examining these complex issues and we stand ready to assist you as we work towards our common goal of protecting patients.

INTRODUCTION

Chairman Harkin, Ranking Member Enzi and members of the committee, thank you for the opportunity to testify today. My name is Martin VanTrieste and I am the senior vice-president of Quality at Amgen, one of the world's leading health care biotechnology companies. We are headquartered in Thousand Oaks, CA and have a significant presence in Asia, Europe and North America, with research, manufacturing, distribution and sales facilities worldwide. Amgen has more than 17,000 employees.

While I bring with me today my experience at Amgen ensuring supply chain security and quality, my testimony today is on behalf of Rx-360, a consortium developed by volunteers from the Pharmaceutical and Biotech industries which includes their suppliers.

Management of the biopharmaceutical supply chain has become one of the top public health concerns with respect to consumer safety. The globalization of distribution for drug raw materials, components, and finished products has introduced many complications that to date have yet to be fully resolved. Unethical players and noncompliant companies along the supply chain can intentionally introduce counterfeited, adulterated and contaminated materials, often with tragic consequences.

Some of these recent tragic events have been well publicized and include:

1. Adulterated glycerin with diethylene glycol (antifreeze) used to manufacture cough syrup has led to 67 deaths in Panama and 103 deaths in Haiti (mostly children).
2. Adulterated Heparin with hypersulfated chondroitin sulfate led to 81 deaths in the United States and Europe.
3. Adulterated milk with melamine has led to contaminated infant formula causing kidney stones and deaths of infants in China.
4. Adulterated glycerin with diethylene glycol used to manufacture teething gel has led to over 40 infant deaths in Nigeria.

The biopharmaceutical industry is extensively regulated by the FDA in a variety of ways, including through compliance with Good Manufacturing Practices (cGMP). However, economically motivated adulteration, like that listed above, is not a Good Manufacturing Practice compliance issue. Good Manufacturing Practices keep the honest people honest but does little to prevent unethical players or criminals from exploiting complexities in the supply chain.

We must realize that it's not a matter of if economically motivated adulteration will happen again, but when and where it will happen.

Given this challenge, leaders in quality from the biopharmaceutical industry came together to find solutions to this problem. We recognized that our standard Quality Systems and Good Manufacturing Practices would not be sufficient to detect such illicit activity. We also quickly recognized that no one company could adequately address this very complex global problem facing our industry, and therefore we needed to collaborate. It is a holistic approach coordinated between industry, regulators and policymakers that is the most effective and efficient manner to deal with this global complex problem. These discussions lead to the formation of a consortium called Rx-360.

RX-360 HISTORY AND MISSION

The formation of Rx-360 was a direct response to the heparin crisis and a call to action by Dr. Janet Woodcock, Director of the Food and Drug Administration's Center for Drug Evaluation and Research, during her keynote address at the first Parenteral Drug Association—FDA Supply Chain Conference. During the fall and winter of 2008, a few quality thought leaders in the biopharmaceutical industry took up this call to action and met to discuss the events around the economically motivated adulteration of heparin. We quickly realized as a group that unethical players and criminals had entered into the biopharmaceutical supply chain in an unprecedented manner that had not previously been seen in the United States and Western Europe.

Our consortium was incorporated in June 2009 with six member biopharmaceutical companies as founding members. This membership has quickly grown to over 65 member organizations, including most of the large Pharmaceutical, Biotechnology and Generic drug manufacturers along with many key suppliers. Rx-360 membership is open to branded and generic biopharmaceutical companies, their suppliers, professional organizations and regulatory agencies.

The purpose of Rx-360 is to enhance the security of the biopharmaceutical supply chain and to assure the quality and authenticity of the products moving through that supply chain. The individuals developing this concept are working in the best interest of patients. We are a non-profit organization with the mission to create and monitor a global quality system that meets the expectations of industry and regulators and that assures patient safety by guaranteeing product quality and authenticity throughout the supply chain.

Broadly speaking, Rx-360 focuses on four areas to secure the supply chain and to assure the quality of materials throughout the supply chain. These four areas are:

1. Adopting standards and best practices;
2. Technology development and implementation;
3. Surveillance around events that could lead to supply chain threats; and
4. Sharing supplier audits.

Rx-360 members recognize that we are responsible for our suppliers and supply chains and have a responsibility to tackle head-on the challenges associated with a global supply chain. With that in mind, Rx-360 member companies have implemented company-specific and collaborative-based initiatives to help further assure a secure supply chain in the interest of product quality and ultimately, patient safety.

PROBLEMS ASSOCIATED WITH A GLOBAL SUPPLY CHAIN

Globalization is impacting most industries and the biopharmaceutical industry is no exception. On the positive side, it has enabled our industry to enter markets all over the world and provide life-saving medicines to millions of patients. With the benefits of globalization, however, come significant challenges and responsibilities. One of those challenges is ensuring the authenticity and quality of materials moving through the supply chain.

Several highly publicized events have highlighted a weakness in the biopharmaceutical supply chain. Significant harm to patients, including death, has been associated with these events. These incidents have led to a loud and swift reaction from the public, biopharmaceutical companies, health authorities and policymakers. These events have shown us how unethical players and criminals have entered into the supply chain, introducing counterfeited, adulterated and contaminated materials, often with tragic consequences.

I have had the opportunity to present on supply chain security at many global conferences with other experts in the field, including representatives from foreign and domestic regulatory agencies. As I conduct my research for these presentations, it can become increasingly unsettling and overwhelming how complex the issues are and the potential problems that exist.

I quickly realized that the challenges presented by a very complex, global supply chain, which spans numerous regions of the world and many regulatory jurisdictions, are too vast to take on at one time or with one solution. It was clear to me that there is no magic solution for these issues, but that working together, the industry, its suppliers, regulators and policymakers can improve the safety of the supply chain.

WHAT RX-360 HAS ACCOMPLISHED TO DATE

These issues and their resolution are of extreme importance to Rx-360 and its members, and are the reason that the organization was founded by dedicated quality experts looking for solutions. Patient safety is not a competitive advantage, and the members of Rx-360 are looking at novel ways to improve the system and have already accomplished a great deal in our short time of existence. Examples of this include:

• **Shared Audits:** Rx-360 is working to implement two shared audit programs; a joint audit program and a shared audit program, which will allow the collection and sharing of audit information of suppliers so that this information can be leveraged across all members of the consortium.

The Board of Rx-360 recently announced positive results from its shared audit pilot program. In the pilot, the biopharmaceutical company which sponsors the audit

and the audited supplier agreed to share redacted audit reports which were uploaded into the Rx-360 database for all members to share. From this pilot program the following benefits were found:

- Shared audits provide a broader, more thorough "picture" of quality culture and performance;
- Existing reports can be used to identify and pre-screen new suppliers; and
- Potential savings with evaluation of reports/responses to reduce supplier audit frequency/length, or audit scope.

• **Joint audits:** Joint audits are designed to increase the effectiveness of each audit by collecting and analyzing more information while reducing the audit burden on suppliers and biopharmaceutical companies. Rx-360 uses qualified third-party auditors to conduct joint supplier audits on behalf of the consortium's members. All auditors are provided the same high-quality training by Rx-360, which ensures that each audit is effective, efficient, and consistent throughout the supplier base.

Once complete, the audit report is placed into an electronic database where Rx-360 members are provided access to the report, in lieu of conducting an on-site audit themselves. This sharing reduces the number of audits that a supplier must host and that a biopharmaceutical firm must conduct itself. This will reduce the overall audit burden to suppliers and biopharmaceutical drug product manufacturers, and provides more information on a particular supplier than previous audits have been able to provide. One additional benefit is that any savings can be re-invested in process and quality system improvements.

One of the Rx-360 supplier members estimates that it costs them $20,000 to host a customer audit, and they receive multiple customer audits a year to host. By having these joint audits, suppliers can save resources and money and apply these savings toward making improvements and not just hosting audits. Most suppliers would agree to allow Rx-360 auditors to spend more time auditing for a shared audit than they would allow an individual biopharmaceutical company.

The joint audit scheme is in the pilot phase, which is planned to be completed by the end of November 2011.

Rx-360 is moving forward towards formally implementing these audit programs and we expect this to be a significant step in improving the ability to ensure supplier quality in a global environment.

• **Adoption of Standards and Best Practices:** Rx-360 has adopted, or is in the final stages of adopting, numerous standards and best practices designed to help secure the supply chain and the security of the materials throughout the supply chain. For example, Rx-360 recently published a points-to-consider document on how to improve security of biopharmaceutical shipments and prevent cargo theft. This information was presented to FDA at a workshop and will allow industry to utilize these techniques to help prevent cargo theft. Many firms have implemented, or are in the process of implementing, these best practices.

• **Development of Detection Techniques:** Rx-360 has developed an analytical technique to detect potentially economically motivated adulteration in response to raw material shortage. We have learned that shortages provide an opportunity for criminals and unethical players in the supply chain to exploit. As an example, once Rx-360 became aware of an acetylnitrile shortage, a key raw material used in active ingredient manufacturing, we rapidly informed our members so they could secure inventory and then developed a method that was provided to everyone and anyone to detect if their raw materials were adulterated for economic gains.

• **Membership Alerts:** Rx-360 regularly alerts its membership regarding potential supply chain issues so that companies and suppliers can implement preventative and corrective measures to quickly avoid issues which have been discovered. These alerts help put members on notice regarding potential problems and also serve to rapidly gather the appropriate experts to respond to known supply chain threats in order to protect patients. For example, in the midst of the Japanese tsunami and nuclear accident, Rx-360 assembled a panel of experts to evaluate the impact on the supply chain and recommend best practices to the biopharmaceutical industry in order to assure the safe distribution of drug products in Japan and how to assure that raw materials and drug product produced in Japan would not have adverse patient consequences.

A STATEMENT OF SUPPORT FOR FDA

Rx-360 is supportive of the FDA's efforts to address economically motivated adulteration, counterfeits, substandard medicines and the Agency's efforts to help ensure the supply chain remains secure. We believe a strong, well-funded FDA is critical to the health and safety of the American public, both for the purposes of helping to assure the safety, effectiveness and availability of medicines and to help ensure

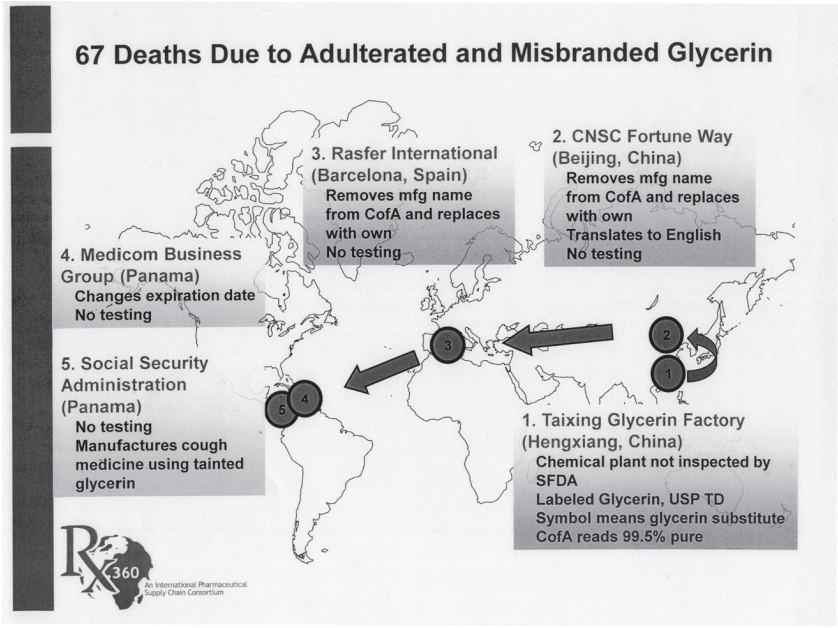
continued access to innovative new therapies for American patients. As such, Rx-360 is supportive of efforts to provide adequate resources to the FDA so that the Agency can enhance its inspection efforts abroad and ensure a safe, secure supply chain.

POINTS TO CONSIDER IN ANY LEGISLATIVE/REGULATORY EFFORT TO IMPROVE SUPPLY CHAIN SECURITY

Rx-360 appreciates that policymakers are examining ways to improve supply chain security and would like to be a resource as you examine these issues going forward. As I mentioned earlier in my testimony, we think that we face a complex, global problem that needs a holistic solution requiring industry, regulatory authorities and policymakers working collaboratively to attack the problem. However, it is important that any legislative or regulatory proposals are carefully considered so as to ensure that there are no unintended consequences, such as adding complexity to an already complex system, unintentionally creating drug shortages, and adding significant cost to the health care system.

The biopharmaceutical supply chain is a complex and global endeavor, and Rx-360 is an example of what can be done when stakeholders work together to address solutions. As you examine these issues some points for consideration which could improve supply chain security include:

• **Ingredient suppliers should disclose the actual manufacturing site to the drug product manufacturer:** There are many potential links in a global supply chain where a series of brokers and distributors could be involved. If we try to learn from the contaminated glycerin events in Panama we must recognize that one contributing factor is that the drug product manufacturer in Panama had no idea that the glycerin they were purchasing was sourced from China since at least three distributors or brokers did not disclose the location of the manufacturing site. As such the drug product manufacturer did not have the opportunity to audit the ingredient manufacturer and had to depend on the Quality Systems of several foreign intermediaries that did not act in an ethical manner. *See attached chart of events leading up to contaminated glycerin*.



• **Foreign ingredient manufacturing sites should be registered with the FDA and only those whose products are actually used in the United States and pay a nominal fee should be allowed to maintain registration:** This will assure that the FDA has an accurate data set to be used for oversight. There are many suppliers who have no intention to distribute product within the United States but use an FDA registration to convey a sense of FDA approval to non-U.S.-

based manufacturers. This behavior only adds misleading data to any FDA database and makes it harder for FDA to achieve their objectives.

• **FDA should inspect foreign ingredient manufacturing sites using a risk-based approach and those foreign ingredient manufacturers should pay the cost of FDA inspections:** The Food, Drug and Cosmetic Act requires the FDA to inspect domestic manufacturers every 2 years, but has no such mandate to inspect foreign manufacturers with such frequency. For over 40 years, overseas manufacturers have had unfettered access to the largest biopharmaceutical market in the world with very little regulatory oversight or inspections. This inspection gap between domestic and foreign inspections should be made up quickly, and funded by the sites external to the United States. According to the recent PEW report, at the current FDA inspection rate, it will take more than 13 years to inspect the sites outside the United States, and that more than 80 percent of the drugs consumed in the United States are now manufactured outside the United States.

Today, U.S. manufacturers who are inspected by many foreign regulatory agencies pay for the cost of these inspections. By requiring foreign manufacturers to cover the cost of FDA inspections, this will assure that the FDA will have adequate funding for inspections and experienced investigators. It would also have adequate funding to assure that the appropriate numbers of investigators participate in a foreign inspection and that the length of the inspection is appropriate to provide adequate oversight. Inspection fees should also provide adequate funding so that FDA Investigators are not asked to bear unreasonable hardships when making travel and lodging arrangements. Also, given resource constraints, perhaps FDA and Congress could consider allowing qualified third-party inspectors to inspect these foreign facilities.

• **Increased criminal penalties for economically motivated adulteration and counterfeiting:** Today, a criminal can make astronomical profits by knowingly engaging in economically motivated adulterating or counterfeiting a biopharmaceutical ingredient or drug product, with little chance of getting arrested and even if they are arrested the criminal penalties are small compared to the crime. FDA and other enforcement authorities should make this a focus for enforcement and criminal penalties should be increased to reflect the gravity of the crime and the life-threatening risks to patients, like those that have been proposed in recent legislative proposals.

We also believe that during FDA overseas GMP inspections, particularly of biopharmaceutical ingredient manufacturers, that these inspections should also focus on good distribution practices and the authenticity of data submitted to the FDA. For example, there are unintended threats, such as improper handling of drugs and raw materials, especially if temperature-sensitive, that can compromise the efficacy and safety of drugs and pose just as serious of an implication to patient safety.

Based on results from risk assessments or suspicious reports from the field, the FDA should also consider deploying specially trained forensic and criminal investigators that can detect fraud, the use of "show" and "shadow" factories, and the potential for economic adulteration, since these skills are vastly different from the skills needed for a routine cGMP inspection.

FDA should also consider whether to monitor or provide special scrutiny to products or ingredients in short supply since these situations may provide additional incentives and opportunities for unethical players to engage in economically motivated adulteration of products.

CONCLUSION

On behalf of Rx-360, I thank the committee for taking on these complex issues in order to protect patients. I am encouraged by the collaboration of all stakeholders working together to address this complex issue. Rx-360 members are dedicated to protecting patients by securing the biopharmaceutical supply chain. This dedication is demonstrated everyday by their and their employee's contributions leading to the remarkable success of Rx-360 in a relatively short period of time. We stand ready to assist the committee as they continue their work on this important issue.

The CHAIRMAN. Thank you very much, Mr. VanTrieste.

And now, Mr. Coukell, if you'll summarize, we appreciate it.

STATEMENT OF ALLAN COUKELL, BScPharm, DIRECTOR OF MEDICAL PROGRAMS, PEW HEALTH GROUP, WASHINGTON, DC

Mr. COUKELL. Thank you, Mr. Chairman, Ranking Member Enzi, and members of the committee. Thank you for the opportunity to

testify. My name is Allan Coukell. I'm a pharmacist and director of medical programs in the Pew Health Group.

We recently released a report called "After Heparin: Protecting Consumers from the Risks of Substandard and Counterfeit Drugs."* Our chief findings are consistent with what you've heard from previous speakers. Pharmaceutical manufacturing is now globalized and increasingly outsourced, and to ensure safety, both the FDA and manufacturers must adjust.

The Pew report is based on published studies and documents and dozens of interviews with experts as well as a 2-day conference that included regulators and a broad representation from industry. We outlined a series of case studies to illustrate the kind of rare but potentially very serious risks we face. We identified systemic problems and practical solutions.

We called the report "After Heparin" both because Heparin was a wake-up call for industry and regulators and because it so clearly shows many of the failings of our current system. For example, the U.S. manufacturer in that case failed to perform a timely audit of its Chinese supplier. The FDA approved the supplier without an inspection, partly because an agency database confused two different facilities. The standard test for Heparin then in use was outdated and not designed to detect a contaminant. There were significant manufacturing quality issues.

And even after the fact, neither the FDA nor the manufacturer was ever able to gain complete access to that upstream supply chain, hindered in part by lack of cooperation from Chinese authorities. Unless you think this is ancient history, I point out that just last month, the FDA issued a warning letter to yet another Heparin facility in China for failing to adequately evaluate suppliers or perform testing.

Others today have stressed the need for increased foreign inspections. It's an area where there's a good deal of consensus, and I'd be happy to expand on what we see as key changes to ensure safety and a level playing field. Speakers have also mentioned the need for manufacturers themselves to ensure quality, and that's crucial.

One speaker at our conference last year was Philippe Andre, a China-based pharmaceutical auditor whose business involves visiting manufacturing facilities in Asia on behalf of United States and European companies. I'd like to show a photo that he shared with us. You can see here—this is a facility in China. And just by the rusted pipes and the broken windows, you know this is not using good manufacturing practices.

Of course, there are very good facilities in China. This just wasn't one of them. But it is the start of the supply chain for a western company.

Sometimes substandard facilities sell to so-called show factories, high-quality facilities that sell products they didn't actually make. And in Mr. Andre's experience, American and European companies are misinformed about the identity of all or part of their supply chain more than a third of the time.

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*The "After Heparin: Protecting Consumers from the Risks of Substandard and Counterfeit Drugs Report may be found at *http://www.pewtrusts.org/uploadedfiles/www.pewtrustsorg/Reports/Health/Pew__Heparin__Final__HR.pdf*.

Our report examines a number of other case studies including where manufacturers falsified or concealed records. And we note the risk of U.S. patients receiving counterfeit or stolen products that penetrate our domestic distribution system.

Mr. VanTrieste has just reiterated—let me reiterate the diethylene glycol poisoning, where the toxic material moved from a manufacturer in China to another broker in China, to a broker in Europe, to a broker in another part of the world. Each time the label is changed and replaced with a new, inaccurate label, and each time the history of the product is destroyed.

Indeed, it was poisoning with this exact same substance that led Congress to pass the Food, Drug, and Cosmetic Act in 1938. The patients who died in the Panama example were largely children. And we must ensure that the FDCA reflects today's reality.

The necessary steps are practical, feasible, and crucial. Many have been included in previous bipartisan legislation before this committee and in Senator Bennet's bill introduced last year. I've mentioned inspections and the need that manufacturers better assess their suppliers, and they're accountable for doing so.

We also need to ensure that testing standards are updated and that the FDA has the tools it needs. For example, many people are surprised to learn that the FDA can't order the recall of a drug product if it's adulterated. They can do it for medical devices and for food, and they should have that authority for drugs. If they have it, it's less likely they'll need to use it. Done well, a regulatory scheme will reward the good players and ensure that the bad actors don't create a race to the bottom.

In conclusion, let me say that Americans support these sorts of changes. Pew commissioned a poll last year which found that likely voters are concerned with drugs from developing countries. And across the political spectrum, they overwhelmingly favor many of the provisions I've outlined. As Congress did 70 years ago, we urge you today to act to ensure safety. We shouldn't wait for another tragedy.

Thank you.

[The prepared statement of Mr. Coukell follows:]

PREPARED STATEMENT OF ALLAN COUKELL, BSCPHARM

SUMMARY

A major focus of the Pew Health Group is identifying ways to address risks to the U.S. pharmaceutical supply chain. In March of this year, we hosted a 2-day conference 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) and State regulators, 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 final report was issued on July 12.

The presenters at our meeting explained that while the vast majority of drugs in our pharmacies and medicine cabinets are not counterfeit or adulterated, pharmaceutical manufacturing has changed dramatically in recent years, becoming increasingly globalized and outsourced. This creates new risks which were dramatically illustrated not long ago with the intentional adulteration of the common blood-thinning drug, heparin.

Despite globalization of manufacturing, FDA oversight is largely domestically focused. The Food, Drug and Cosmetic Act (FDCA) requires inspections of U.S. plants

every 2 years, but specifies no inspection frequency for foreign plants. The FDA lacks the resources to inspect foreign sites with any meaningful regularity. 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.

Poor adherence to quality standards has been observed both in the United States 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 percent of a factory's operating costs. 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.

Additional legislative changes are now needed to give the FDA the tools it needs and 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.
2. Overseas inspections by FDA must be significantly increased.
3. FDA authority and enforcement gaps must be addressed.
4. Improve the information flow to FDA.

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 2-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 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 adequately assess suppliers. Although the firm in question was supplying the U.S. 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 United States 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 percent of all finished pharmaceuticals,[14] and 80 percent 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 United States is the No. 1 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 $1 billion or more. Ninety-four percent of those surveyed saw their greatest supply chain risk as raw materials sourced outside the United States.

Despite globalization of manufacturing, FDA oversight is largely domestically focused. The Food, Drug and Cosmetic Act (FDCA) requires inspections of U.S. plants every 2 years, but specifies no inspection frequency for foreign plants.[18] The FDA lacks the resources to inspect foreign sites with any meaningful regularity.[19] 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.[20]

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 United States 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 percent of a factory's operating costs.[21] 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 United

States that they claimed to have made at their own factory, but was in fact made entirely at two external plants.[22] The FDA has said that some of this heparin may have contained the same contaminant associated with the deaths in 2007 and 2008.[23] 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.[24] [25] In 2010, another Indian manufacturer was found to have falsified batch manufacturing records for an anti-platelet medicine. EU 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.[26]

In Panama in 2006, dozens of people died after taking a cough medicine that had been made with diethylene glycol,[27] [28] a sweet-tasting, but poisonous solvent.[29] 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.[30] 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.[31] 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 United States 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.[32] 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.[33] 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 entities.

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.[34] And Americans across the political spectrum overwhelmingly support giving FDA increased authority in order to protect the domestic drug supply. For example, 86 percent of respondents supported inspecting foreign facilities every 2 years; 94 percent 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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The CHAIRMAN. Thank you very much, Mr. Coukell, and we'll begin a round of 5-minute questions.

Starting with Dr. Crosse, in the past, you reported that FDA databases—and I heard this from others here too—had contained incorrect information about foreign drug establishments. What's the reason for this, and is this still the case, that they contain incorrect information?

Ms. CROSSE. It is still the case. There are several reasons. You heard Ms. Autor speak about a paper-based registration system that previously existed. Now, FDA has gone to an electronic system which has reduced certain errors of data entry, but they still don't have in place a requirement for any sort of unique identifier for a facility.

They ask companies now with this electronic registration that they submit a unique identifier, a Dun and Bradstreet D-U-N-S number, that they can enter into the system. They cannot require companies to submit that, and while many are complying, perhaps some of the ones you'd most want to have information about may not be complying with that.

But, nevertheless, you continue to have other systems that are populating FDA databases with incorrect information. When shipments arrive at the border, the Customs and Border Protection has a data system that does not use a unique identifier, and that then sends incorrect information to FDA.

The CHAIRMAN. So this is a question for all of you. Should we have a requirement that any finished drug, any ingredient or excipient that is manufactured in a foreign country that comes to this country have a bar code attached to it at all levels? Now, we know that they very seldom—they don't go directly from a small plant like that to some pharmacy in the United States. They go through different brokers here, in Spain, as you pointed out, and Canada and other places like that.

Should we require that every one of those three that I mentioned—that they have a bar code attached to it so that it can be

immediately traceable back to its origin, back to the very plant where it started? Is that possible to do, and should we do it?

Dr. Crosse.

Ms. CROSSE. I'm not sure about the feasibility of that. I think until you get data systems aligned between Customs and Border Protection and FDA, you may still have problems with inaccurate information showing up from one agency to another.

The CHAIRMAN. Well, I'm just asking if that one plant has to put on—no matter what it is, they have to put on a bar code, and that has to follow that all the way through to the final purchaser.

Dr. Martello, is that possible?

Ms. MARTELLO. I can't speak to electronic—to the feasibility of that. My sense is that would be a significant cost and complexity added to the distribution system that may be challenging for folks to comply with. I think we do have a strong—very strong system today, and we should look for opportunities to make that stronger. But I worry about the cost and complexity of such a system with so many independent actors in the supply chain.

The CHAIRMAN. OK. I'm just asking for a simple bar code at every step of the way.

Mr. Johnston, what do you think? Is that possible?

Mr. JOHNSTON. Well, GPhA members looked at bar codes for track-and-trace purposes in the United States.

The CHAIRMAN. Exactly.

Mr. JOHNSTON. And doing it domestically, we've seen the feasibility, I think, as being probable, because you can utilize integrated technologies, and we can have manufacturers, pharmacists, wholesalers on the same page. Some of the challenges are, when you get into international regions, finding this harmonization so that the same bar code, the same readers, the same technologies all apply.

So when it comes to the international scope, I think there's issues there that would have to be looked at to make sure that the viability of a bar code applied in China would be read all the way through the system and that data would be available to the end user. So there's challenges there.

The CHAIRMAN. Mr. VanTrieste.

Mr. VANTRIESTE. Well, I think the use of bar codes is definitely possible. We see it in supermarkets. I think the complexity comes in with the integration of this data from a worldwide perspective and how long that would take to be actually implemented.

I think you can get to the end result you need by requiring everybody in that supply chain to tell the final person who's going to use that raw material—the pharmaceutical manufacturer—who that original manufacturer was. The pharmaceutical manufacturer can then provide the oversight of the entire supply chain once they know it. If we don't know it, then we know we've got a problem. So I think just requiring that transparency and disclosure will get to where you want to go much faster.

The CHAIRMAN. Mr. Coukell.

Mr. COUKELL. I agree. I think the underlying principle here is that manufacturers need to know their complete supply chain. They need to have confidence that the quality standards are in place and that the FDA has to be able to get access to that data if they need it. We need a way for everybody to be on the same

page about which facilities we're talking about. Whether it's a bar code or some other means, I think, matters less.

The CHAIRMAN. Thank you all very much.

Senator Enzi.

Senator ENZI. Thank you, Mr. Chairman.

Mr. VanTrieste, your testimony suggests that poorly designed supply chain reforms could exacerbate drug shortage problems. Could you elaborate a little bit?

Mr. VANTRIESTE. Yes, of course. As we all talked earlier about, if we increase regulation, certain players who are in the business today may decide to get out of the business. They might be the only supplier of a key ingredient for a critical medicine to treat patients.

So any legislation that we do, I think we have to give the secretary some latitude to prevent those suppliers from exiting the market and give them enforcement discretion on where to apply the regulations, because we don't want to see people exit the market who are sole suppliers.

Senator ENZI. Thank you.

Dr. Crosse, what's wrong with the FDA's drug supply chain information systems, and what does the FDA need to do to fix them?

Ms. CROSSE. Well, there are several problems. They have a long history of poor information technology systems, and they're in a process now of trying to upgrade those systems across the board, across the entire agency. That's taking several years, and it's encountered many difficulties in trying to integrate what had been a number of different freestanding systems that weren't compatible.

I mentioned just a moment ago one of the problems is that some of the key information they get comes from another agency, from Customs and Border Protection, which is not providing accurate information in many instances because of the way certain identifiers are generated in that system. FDA has been taking some steps to try to verify information that they have.

They've actually hired contractors to go now and look at certain suspect facilities to see if they're actually located where they've told FDA that they are. And they've found a number of facilities that are not at the locations that they've reported. But it's taking FDA a very long time to try to go through and make up time on these systems, and they still don't all talk to one another.

Senator ENZI. Thank you.

Dr. Martello, can you give us an overview of your member companies' quality control systems? Do they customarily audit or inspect their suppliers?

Ms. MARTELLO. Thank you for that question. The quality systems approach is really embodied in the current good manufacturing practice regulations, and our companies take great steps to comply with those. The GMP regulations require that each facility have in place a quality control unit that's responsible for all aspects of the manufacture of a drug product, for all control of all incoming ingredients, and periodic testing throughout the process. And taken with the new drug approval requirements, the cGMP requirements in our closed distribution system help provide assurances that the medicines that patients take are safe and have the identity and the quality that they are purported to represent.

Senator ENZI. Thank you.

Mr. Coukell, Pew supports mandatory recall authority for drugs. How many times has a drug manufacturer refused FDA's request to conduct a voluntary recall?

Mr. COUKELL. Thank you for the question, Senator. I can give you an example, in 2008 when the FDA had to go to court to get some contaminated Heparin off the market. I think the bigger concern is not the refusal, but if public health is at risk, the time it would take if the FDA does have to go to court. It's the kind of authority that, if they have it, I think it will bring everybody to a consensus much more quickly about whether a voluntary recall is necessary.

Senator ENZI. If a manufacturer refuses to conduct a voluntary recall, how does making it mandatory help?

Mr. COUKELL. I presume that there would be some sanction involved for refusing to do a mandatory recall.

Senator ENZI. Mr. Johnston, the law requires FDA to inspect domestic drug establishments every 2 years. But the law is silent about how FDA must inspect foreign establishments. Can you elaborate on the need to level the playing field?

Mr. JOHNSTON. Thank you, Senator Enzi. There's two components, I think, to answering that question, the first being the parity, that foreign establishments should be inspected at the same level, intensity, and frequency as domestic facilities. There's a substantial cost for inspections to drug companies.

And I might use the example of companies sitting in Philadelphia or New Jersey. They have FDA visiting each month or every other month. And it takes resources, time, personnel to accommodate these inspections.

The contrast is foreign inspections, when companies or facilities are visited on a 3-, 4-, or 5-year basis. There's additional cost to the American industry and, more importantly, to the public health. By having equivalents in terms of inspections, FDA has the opportunity to evaluate these foreign facilities, determine if there are any GMP or quality problems, supply chain issues, and have those addressed in a timely basis. So bringing comparability into inspection requirements, we believe, is a very important component of supply chain security.

Senator ENZI. Thank you, and my time has expired. I have questions I'll submit.

The CHAIRMAN. Thank you, Senator Enzi.

Senator Franken.

Senator FRANKEN. Thank you. I'll try to be fast because I know Senator Bennet has to get out of here and I have to preside in a few minutes.

Dr. Martello, as we heard from Mr. Johnston, the generic pharmaceutical companies are working with the FDA to do their fair share and provide the FDA with additional resources to increase foreign inspection and capacity. While I realize that the brand name companies don't occupy as much of the market as the generics do, would your member companies be willing to contribute to securing the supply chain through increased user fees?

Ms. MARTELLO. Thanks very much for that question. I think it's important to recognize that since 1992, the PDUFA user fees—prescription drug user fees that we're looking to reauthorize next year

actually have supported preapproval inspections since their inception in 1992. And as the GAO has reported, the majority of facility inspections that are conducted are both preapproval and GMP inspections combined. So our industry is really committed to this issue and has supported inspections in the form of the user fees as a portion of that since 1992.

We also think and we recognize that, frankly, there will never be enough resources for the agency to get to all the places that they need to get. And so that's why we believe that using a risk-based approach for FDA to target facilities for inspection and really focus on the areas of highest risk will help do a great deal. You could couple that with reliance on third parties, again, whether it be accredited third parties or foreign regulatory authorities with competent regulatory systems.

Using those things together, we can expand the reach of the FDA and help them do their job by focusing on the areas of highest risk and really increasing the number of facilities that the FDA is visiting on a routine basis.

Senator FRANKEN. I guess I didn't totally understand your answer.

Mr. Johnston, do the generics put more resources into the supply chain, helping FDA with the supply chain?

Mr. JOHNSTON. Thank you. The user fee proposal that FDA is considering—and I think we've reached agreement on—doesn't specify how many of the resources go into inspections. However, there are performance goals that will certainly drive the utilization of the resources toward inspections. And, as we heard, 80 percent of the incoming materials are foreign and 40 percent of the products. FDA will dedicate probably 40 or 50 percent of the user fee resources from the generic industry toward inspections and support for those inspections.

Senator FRANKEN. And, I guess, Dr. Martello, I was asking are you willing to put in more toward that end?

Ms. MARTELLO. User fees have gone to support preapproval inspections since their inception in 1992. The PDUFA——

Senator FRANKEN. Preapproval inspections—what do you——

Ms. MARTELLO. Preapproval—when a company files a new drug approval application, the FDA has the discretion to go and inspect—the preapproval inspection——

Senator FRANKEN. OK. I'm not talking about preapproval. I'm talking about supply chain, foreign supply chain.

Ms. MARTELLO. Many times, as the GAO has found, a preapproval inspection is coupled with a good manufacturing practice inspection. So the facilities that are filing new drug approval applications with the agency are getting those inspections on a regular basis, and they are supported through the user fees in the Prescription Drug User Fee Act provision.

Senator FRANKEN. OK. Would PhRMA be willing to put more in to do that, to secure the foreign supply chain? I think that's what I've been asking you, and I don't quite feel like I'm getting a real answer. I feel like I'm getting a circular kind of answer.

Ms. MARTELLO. Across the board, the Prescription Drug User Fee Act and the agreement that was just released increases resources

for FDA to conduct the necessary reviews of new drug approval applications.

Senator FRANKEN. Well, that's new drug approval.

Ms. MARTELLO. And with that, a portion of that is targeted for inspections.

Senator FRANKEN. What about existing drugs?

Ms. MARTELLO. Our companies do our fair share to try to——

Senator FRANKEN. Would you do more?

Ms. MARTELLO. I think we'd be happy to engage in conversations around that. We think giving the FDA the opportunity to use risk to drive the intervals at which they inspect facilities will help expand their reach and help them maximize and use their resources efficiently, because we know that resources are not unlimited.

Senator FRANKEN. Thank you.

Thank you, Mr. Chairman.

The CHAIRMAN. Thank you, Senator Franken.

Senator Bennet.

Senator BENNET. Thank you, Mr. Chairman. And, again, I really want to thank you for holding this hearing. This is an issue that I've been working on ever since I got here, and now I know why. The testimony, I think, has been excellent today, and I'm familiar with the work that everybody here has done.

I find remarkable the degree of consensus around a lot of the issues that we face, and I think it reflects how big the gap is between a statute that was written in 1938 and the world as we're living in it today—the changes that are accelerating because of the strengthened global economy that we face. And this lack of an update—or our lack of a regulatory regime that reflects reality is bad for our consumers and it's bad for our business, and I think that's why we need to be urgent in fixing it.

It's been remarkable to read some of the polling data around us, and then the mandatory recall suggestion, for example—first of all, everybody thinks the FDA already has that. They don't. Ninety-four percent of the American people support it, and they believe that when they walk into their grocery store or their pharmacy that their drug has been likely produced in the United States. That's not true.

And they believe that somebody has looked at it to make sure that it's safe. That's not true, either. In fact, what we've learned from the testimony today is that even if we discover that there's a problem, it's hard to track it down to the source in China. So there's a lot of work to do here, and whatever I can do to help you with it, I want to do.

I'd like to ask Mr. Coukell first and then let anybody else from the panel answer—I just have one question. Pew has done some great work on this "After Heparin" report that you talked about. I think it's very important. And in that report, it made the observation that compliance with internal quality systems and regulations can represent up to 25 percent of a finished drug manufacturer's operating costs.

And at the same time, as we heard from Ms. Crosse at GAO, it would take FDA 9 years to inspect the foreign facilities. So you begin to add this stuff together and ask yourself about an American manufacturer here who's following good manufacturing prac-

tices and still can expect a surprise inspection every 2 years from the FDA—maybe more frequently than that—versus a foreign firm that will never be inspected or may never be inspected, doesn't have to follow any of these practices, and on top of everything else, when they are inspected, as we heard in the testimony of the first panel, they're given warning that the inspectors are coming.

Mr. Coukell, what do you think the three or four most important things are that we can do to level this playing field and make sure that we are protecting both the safety of our citizens, which is the most important thing, and also the playing field for American business which is a vitally important part of our economy?

Mr. COUKELL. Senator, thank you for the question and for your continued commitment to this issue and this area. I think you make a very important point. So the good actors, whether they be in the United States or outside the United States, are spending time and resources to make sure that their manufacturing is sterile, consistent, and predictable and high quality.

And so if you have somebody out there who is tempted to cut corners and not do things to a high standard, and there's no chance that anyone is going to show up and hold them to the high standard, then they can do that. And so that does create an uneven playing field.

So we absolutely need a system where we take the existing inspection or resources and deploy them in a way that the highest risk facilities, wherever they are, are getting inspected and that we're taking steps to make sure that finite resources are stretched so that we aren't inspecting the same facilities that the Europeans are inspecting twice in a year, when someone out there is not getting inspected, where we're relying on additional sources of information, and where the manufacturers themselves are providing better documentation when they're taking all the right steps.

And, again, if you're an importer, and you have something coming into the country, it costs you money if it sits there in the Customs. Meanwhile, the FDA is dealing with—how do we screen all the stuff that's coming in? So if we have a system where the FDA can say, "Yes, they're showing us that this is good quality stuff. Let's get it in the country"—meanwhile, they can focus on the bad actors—that benefits everybody.

Senator BENNET. I just have one second left. Does anybody feel compelled?

Mr. VANTRIESTE. I think, Senator, the one other thing—you talk about leveling the playing field. When I'm inspected by a foreign entity, even the Europeans, I have to pay for that inspection. So why aren't ingredient manufacturers in foreign countries who get FDA inspections required to pay for those inspections to help justify the resources needed to do that?

Senator BENNET. Thank you.

Thanks, Mr. Chairman. Well, I would say I'm sorry Senator Mikulski has left, because in the spirit of what she said, I couldn't agree with her more. And I think it would be surprising—several of you talked about enforcement too, which I would add to the list. I mean, the idea that the penalty for counterfeiting drugs is lower than the penalty for counterfeiting a DVD, for example, Mr. Chair-

man. It just doesn't make any sense to anybody that's living in Colorado and it shouldn't.

Those are the kinds of common sense things that I think we could fix if we get the chance to do it. So thank you for your leadership.

The CHAIRMAN. And thank you also for your leadership, Senator Bennet.

Thank you all for being here. I'll just close by saying that this committee is committed, I think, on a bipartisan basis to move ahead in this area. I don't know that we have crystallized exactly what it is that we want to do. We are seeking information from all of the players in the field out there, from the companies, pharma, generics, FDA, others, to come up with the best formula that we want to put in the PDUFA reauthorization next year.

Again, I just simply need to know why it is that we can't have a system that doesn't cost a lot. It'll cost something. I understand that. But I think indications are that consumers are willing to pay a little bit more for heightened security of the products they're buying—in this case, drugs—to ensure that inspections are held and that companies are held to the highest standards of good manufacturing practices, that there's a transparency to the system.

Mr. VanTrieste, if your research staff could go back and find out where that Heparin came from, which you've done—and yet I hear from Mr. Coukell that no one has ever been held accountable. So, obviously, there's a way of traceability. We need to know—everybody along that line needs to be held accountable. Everybody along the line needs to be held accountable. And the only way you can be held accountable is to know who you are at every step of the way.

That's my question on the bar codes or some other similar situation like that, that we can do that. An interesting point, I think, was raised—I forget who raised it—about coordination with other countries, Europe and others, so that, No. 1, we can assure that manufacturing facilities in supplier countries are inspected. We want to ensure that they're inspected, but we don't want to be duplicative. We don't want one country that inspects it, then another country, then another country. We want to make sure that we have some coordination with other countries in that process.

While I support mandatory recall, that's sort of after the fact. It's fine to have that, but it seems to me that we want to get in front of that so that if there's any indication at all that we can go right back to the source and correct that at the source as soon as possible and to have penalties.

It just boggles my mind that we have some data and information that companies that have supplied dangerous products in this country, they leave that building and they move across the street or they move to another community and they open up a facility, but we have no traceability whatsoever as to who they are. And yet they can continue to sell their products.

So traceability, the enforcement of good manufacturing practices, more of a general agreement among countries on inspections, and making sure that—as you said, Mr. VanTrieste, if you're inspected, you've got to pay for it because you're shipping to other countries, European countries. Well, it seems to me this—again, if they want

to ship to this country, they should, No. 1, allow inspections, and as you've pointed out and I think Ms. Autor pointed out and Dr. Crosse, a lot of times these are delayed. They're put off. They're put off. They're put off for year after year after year.

And the third thing is that I'm very much leaning toward this idea of more of a risk assessment. In other words, there are companies that have good manufacturing practices. They've been in business for some time, and yet we, by law, say they've got to be inspected every 2 years. Maybe they don't need it. Maybe we need to use that personnel to go after the plants that haven't been good actors or new plants that haven't been inspected at all.

So these are all the things that this committee is going to be looking at. We appreciate all your testimonies, and we would appreciate any further input, advice, or consultation you have with us as we proceed on this. I'm committed to doing this sometime next year, because we have to reauthorize PDUFA. And we didn't get into medical devices—but PDUFA, anyway—and the medical device user fee act.

And keep in mind—is there a fee? Is there something that should be attached to a product, an ingredient, or a finished product, that would go for only one purpose and that is to FDA for inspections and enforcement? If you have thoughts on that, please submit them to the committee.

Well, without further—thanks again. I appreciate you all being here. I thought it was a great hearing. And, believe me, we'll be having more. So I request that the record be kept open for 10 days to allow Senators to submit statements and questions for the record. And with that, the committee will stand adjourned.

Thank you very much.

[Additional material follows.]

ADDITIONAL MATERIAL

PREPARED STATEMENT OF HEATHER BRESCH, PRESIDENT, MYLAN INC.

As the largest global generics company headquartered in the United States, Mylan Inc. ("Mylan") appreciates the opportunity to submit comments to the Senate Health, Education, Labor, and Pensions Committee as part of the committee's hearing entitled, *Securing the Pharmaceutical Supply Chain* on September 14, 2011. Ensuring the safety of our Nation's pharmaceutical supply is of critical importance to all Americans and to Mylan, and we thank Chairman Harkin, Ranking Member Enzi and the committee for holding this hearing on such an important topic.

Our company was founded 50 years ago in a small town in West Virginia, and since that time has established one of the industry's broadest and highest quality pharmaceutical product portfolios and now serves as the largest global generics company in the world headquartered in the United States. Today, 1 out of every 11 prescriptions dispensed in the United States, brand or generic, is a Mylan product, and we are proud of the investments we make in all of our facilities around the world to deliver high quality products and more affordable access to patients.

As president of the 3d largest global generics company in the world, I have a strong interest in making sure the competitive playing field in the United States is level and that all facilities supplying the U.S. pharmaceutical market are subject to the same high quality standards. As a mother of four, I want to know that no matter what medicine I give my children, each product, branded or generic, meets one high quality standard regardless of whether the medicine is made inside the United States or outside its borders.

Over the last 4 years, Mylan has gone from a U.S.-based company to a global one, and we now deliver products to customers in more than 150 countries and territories around the world. In operating multiple facilities around the globe, we've discovered that FDA is governed by an outdated law written in 1938 that has not been updated to equip the FDA with the authority it needs to oversee the now globalized U.S. pharmaceutical supply chain. We've also realized that FDA resources have not kept pace with the significant increase in workload and the increase in the number of foreign facilities supplying the U.S. marketplace. The end result is an unlevel playing field and inconsistent application of quality standards for pharmaceutical products sold in the United States. For these reasons, Mylan urges Congress to introduce a bill to update the Federal Food, Drug and Cosmetic Act of 1938 (the "FDCA") to equip the FDA in carrying out its mission in the globalized U.S. pharmaceutical marketplace. Further, we urge Congress to ensure a level playing field for all players participating in the U.S. pharmaceutical supply regardless of their location.

As this committee heard from FDA and others during the September 14, 2011 hearing, the FDCA, which is the key law that gives FDA authority to demand evidence of safety and conduct facility inspections, does not take into account the global nature of today's U.S. pharmaceutical marketplace. FDCA is written as if all participants in the drug supply are domestic based. As the committee also learned, FDA estimates that up to 40 percent of finished drugs consumed by U.S. patients are manufactured abroad and 80 percent of the active ingredients and bulk chemicals used in drugs come from foreign countries.

With a mission to protect and promote public health, FDA has a critical responsibility to ensure the safety, efficacy and security of the U.S. drug supply. Fulfilling this responsibility today is much more challenging than it was in 1938 when the FDCA was enacted. Back then, most of the pharmaceutical products consumed in the United States were produced in the United States. Now, a substantial proportion of those products come from abroad, yet FDA's governing statute still presumes the domestic 1938 landscape.

In particular, the FDCA requires American manufacturers associated with pharmaceutical production to undergo a surveillance inspection at least every 2 years to ensure that these facilities are complying with a rigorous set of standards known as Good Manufacturing Practices (GMP). These extensive on-site inspections conducted by FDA serve as an important mechanism for FDA to ensure facilities are continuing to meet GMP standards. However, the FDCA does not impose the same biennial GMP inspection requirement on foreign facilities. Instead, the law written in 1938 is silent when it comes to foreign manufacturers. Meantime, FDA estimates that foreign facilities supplying the U.S. pharmaceutical marketplace have grown by 185 percent from 2001–8, while at the same time FDA facility inspection rates have

decreased nearly 57 percent.[1] According to a 2010 Government Accountability Office (GAO) report, FDA inspected just 11 percent of the 3,765 foreign establishments in its database in 2009.[2] As a result, the average FDA ex-U.S. facility inspection occurs every 9 years compared to every 2 years for U.S.-based facilities, according to the 2010 report by GAO. According to GAO, some FDA-registered facilities whose drugs are imported into the United States may have never had a GMP inspection.

UNLEVEL PLAYING FIELD IMPACTS MANUFACTURER COMPETITIVENESS

The disparity in the degree of oversight experienced by domestic versus foreign facilities reduces American competitiveness by creating an unlevel playing field as compliance with quality systems and regulations are estimated to make up approximately 25 percent of a drug manufacturer's operating costs.[3] Mandating FDA risk-based biennial GMP inspections of all facilities, foreign and domestic, will improve quality and create a level playing field, allowing U.S. pharmaceutical manufacturers to be more competitive. Leveling the playing field through inspection parity will also benefit foreign facilities and first time entrants who are currently experiencing delays in gaining approval for new products due to a lack of inspection history and a significant gap in FDA resources to address the substantial growth in foreign facilities supporting the U.S. pharmaceutical supply.

IMPERILED DRUG SAFETY

In addition to an unlevel playing field for manufacturers, the glaring disparity between FDA's oversight of foreign facilities versus U.S.-based facilities places the Nation's drug supply at risk. As the committee discussed during the September 14 hearing, a telling example involved tainted Heparin distributed in the United States a few years ago. FDA traced the adulteration of the brand product to a manufacturing facility in China, which the agency had never inspected.

While FDA inspections alone are not the only way FDA ensures safe products, FDA has indicated that routine GMP surveillance inspections are one of the most effective ways to detect noncompliance with GMP standards on the front end to prevent recalls, market disruptions, as well as risks to patient safety.

SUPPLEMENTAL RESOURCES FOR FDA

As the Generic Pharmaceutical Association noted in its remarks before this committee, the generic drug industry, which accounts for 75 percent of all prescription drugs dispensed in the United States, has stepped up to help provide FDA with additional resources to address the challenges caused by the global drug supply and the increase in FDA workload. Even though the historical focus of user fees has primarily been on getting products approved in a timely fashion, given the global challenges of today, the generic industry took the opportunity during its generic user fees negotiations with FDA to incorporate the concepts necessary to help globalize the agency.[4] Following the final review by the Department of Health and Human Services and the Office of Management and Budget, Congress should be receiving the detailed goals letter and legislative language (including fee structure) agreed upon by industry and FDA.

CONCLUSION

In summary, Mylan commends the Chairman, the Ranking Member and this committee for its commitment to addressing this important issue. We are encouraged by the committee's statements and urge you to move forward with introducing legislation to amend the FDCA in order to equip FDA with the authority and scope it needs to carry out its important public health mission of ensuring the safety of to-

[1] Deborah M. Autor, Esq, Director, Office of Compliance, Center for Drug Evaluation and Research, FDA, E*nsuring the Safety, Efficacy, and Quality of Drugs*, Pew Roundtable on Ensuring the Safety of the U.S. Drug Supply, March 14–14, 2011.

[2] U.S. Government Accountability Office. Drug Safety: FDA Has Conducted More Foreign Inspections and Begun to Improve Its Information on Foreign Establishments, but More Progress Is Needed (Publication No. GAO–10–961). (September 2010)

[3] After Heparin: Protecting Consumers from the Risk of Substandard and Counterfeit Drugs at 27. Pew Health Group Report (July 2011). According to the Pew Report, "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. 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."

[4] These negotiations were scheduled by FDA to coincide with the upcoming 2012 congressional reauthorizations of the Prescription Drug User Fee Act and the Medical Device User Fee Act.

day's globalized U.S. drug supply. These important changes to the FDCA will not only result in a safer drug supply with consistent oversight for all players in the U.S. drug system, foreign and domestic, the changes will also help reduce approval times of new drugs undergoing FDA review and expedite the availability of new medicine into the marketplace. This is a particularly important result given that drug shortages are increasingly occurring in the United States due in part to weak links in the supply chain. Also of significance to this committee and many others, these changes will level the playing field for manufacturers, increase competitiveness, and reverse the current incentive in place to move manufacturing abroad.

PREPARED STATEMENT OF DALE CARTER, CHAIR, INTERNATIONAL PHARMACEUTICAL EXCIPIENTS COUNCIL—AMERICAS (IPEC—AMERICAS)

Chairman Tom Harkin, Ranking Member Michael Enzi, and members of the Senate Health, Education, Labor, and Pensions Committee, as the chair of the International Pharmaceutical Excipients Council—Americas (IPEC–Americas), I, on behalf of IPEC–Americas, appreciate this opportunity to submit written testimony and thank you for the leadership you have displayed in addressing the crucial need to secure the pharmaceutical supply chain.

IPEC–Americas helped create a federation of four independent regional industry associations, with the others headquartered in Europe (IPEC Europe), Japan (JPEC) and China (IPEC China). Our goal is to ensure current Good Manufacturing Practices (cGMP) to meet high quality standards for excipients, more commonly known as the inactive pharmaceutical ingredients. IPEC Federation members include over 300 national and multinational excipient makers and users, including chemical companies, pharmaceutical manufacturers, and food companies. These members include over 60 U.S. companies that belong to IPEC–Americas and other members of the Global IPEC Federation.

Each regional association focuses its attention on the applicable law, regulations, science, and business practices of its region of the globe. The four associations work together on excipient safety and public health issues, in connection with international trade matters, and to achieve harmonization of regulatory standards and pharmacopoeial monographs.

We are also the premier source for regulatory and guidance documents critical to the excipient industry; offer training and consulting services to ensure regulatory compliance worldwide; and provide awards to encourage research and education in excipients. Our guidance documents have been adopted and relied upon by various regulatory bodies and standard setting organizations, including the Food and Drug Administration (FDA) and the United States Pharmacopeia.

While attention to the pharmaceutical supply chain has generally been focused on active pharmaceutical ingredients (APIs), we were pleased to note an interest in the supply chain of pharmaceutical excipients in your September 14, 2011 hearing. As was noted by Chairman Harkin and Deborah Autor, Deputy Commissioner for Global Regulatory Operations and Policy at the FDA, it was the death of 100 people from an adulterating excipient, diethylene glycol, that led to the enactment of the Federal Food, Drug and Cosmetics Act (FFDCA) in 1938. Yet, as was also noted, 570 people have died from the same substance in the past 20 years worldwide. As recently as 2009, more than 80 infants died from adulterated teething syrup contaminated by diethylene glycol in Nigeria. These are no small threats to the United States as the pharmaceutical supply chain becomes more and more globalized.

Commissioner Autor noted a number of safeguards with which IPEC agrees and which should apply to both APIs and excipients: enacting legislation that gives the FDA the authority to refuse the importation of drugs into the United States if a facility does not allow itself to be inspected; requiring proof that a product is "good" to enter the United States, rather than FDA having to find something wrong; leveling the playing field by providing requirements and incentives for all companies to follow the rules; and ensuring that manufacturers have adequate control over the supply chain.

IPEC fully supports each and every one of these goals and has drafted legislation to do so. Our proposal would direct the FDA to recognize accredited third-party auditors to certify that manufacturers, distributors and importers of excipients meet safety standards that are in compliance with the FFDCA. The legislation would also call for the establishment of qualification standards for third-party auditors and certifiers who have the necessary expertise and training in auditing techniques. IPEC has been working with FDA to develop appropriate third-party audit requirements for excipients. This effort is integral to IPEC's 20-year effort to develop and maintain high industry standards for excipient safety and quality.

To give real teeth to the FDA, IPEC's proposal would mandate that individuals or companies not be allowed to import into the United States a drug or excipient used in the manufacture of a drug if the product or ingredient was manufactured or produced outside of the United States by an entity which has not been certified by the FDA or by an FDA-recognized third-party auditor.

IPEC is a "coalition of the willing"—member companies who want to ensure the safety and efficacy of excipients and have put mechanisms in place to do so. However, there are actors out there who are not as willing and present a serious threat to the security of the excipients supply chain. Our proposal would require that companies follow cGMP and therefore prove that the excipient products are "good." This in turn would level the playing field, requiring that all companies be compliant, rewarding good products with entry into the United States and turning away those that are not.

Third-party auditing and certification also addresses the need for manufacturers to have adequate control over their suppliers and the supply chain, which, as Commissioner Autor noted, is necessary because the FDA simply does not have the resources to monitor all manufacturers, users, and distributors of excipients. Third-party certification, which would be funded by companies wishing to import into the United States, would provide those resources in a mechanism that is revenue-neutral to the Federal Government.

In short, the proposal would provide the same powers to FDA that Congress recently provided the agency as it relates to contaminated food, but that it still lacks for drugs: the power to keep contaminated or adulterated products or ingredients from reaching the pharmaceutical production process.

We ask that the committee and the full Congress adopt our proposal for a third-party auditing and certification process to ensure the safety of U.S. citizens.

PREPARED STATEMENT OF KEITH NALEPKA, VICE PRESIDENT, BUSINESS DEVELOPMENT, HI-G-TEK, INC.

THE NEED FOR AN ACTIVELY MONITORED AND SECURED PHARMACEUTICAL SUPPLY CHAIN

Chairman Harkin, Ranking Member Enzi, and members of the committee, with a growing interest among thieves to target high value pharmaceuticals and biologics there needs to be a change in the way industry approaches supply chain security and monitoring. There continues to be a direct correlation between these thefts and counterfeit production as well as an increase in stolen product being shipped and sold in developing countries and also re-entering the U.S. supply chain.

The pharma supply chain is incredibly complex, with products being sent through multiple touch points. The adoption of passive RF1D, bar coding of all types, e-pedigree and others does nothing to actively secure or monitor the supply chain. Thieves are long gone with the stolen goods and are becoming increasingly adept at reproducing all of these passive tags for re-entry into the supply chain or producing incredible look-alike products used internationally. They provide no data that can be used to repair a defective supply chain or increase security.

The FDA is in the process of making swift changes in the pharma supply chain. The recent problems with the heparin and acetaminophen supply chain catastrophes have drawn attention to areas in the supply chain that arc vulnerable. Slow recalls can no longer be tolerated, and chain of custody documentation will become an absolute necessity.

The solution can be found by monitoring shipments actively, in real time. The successful documentation of temperature, light exposure, humidity, open/close, tilt, and package tampering with sensors needs to become a best practice. Being able to intervene midstream with a package in transit that is experiencing a temperature excursion could save efficacy and patients in the long run. Being able to see in real time a potential theft by the tripping of a sensor could provide added security and visibility into the supply chain. Lastly, being able to collect these biometric data points and put them in document form that can show chain of custody down to the package level would he invaluable when an FDA audit occurs. Being able to initiate a recall in real time also provides added patient safety. Having this biometric data would provide the ability to fix areas in the supply chain that may be common avenues for temperature excursions, theft, etc. Without active data it's much more difficult to take action.

PREPARED STATEMENT OF THE AMERICAN SOCIETY OF HEALTH-SYSTEM PHARMACISTS

The American Society of Health-System Pharmacists (ASHP) respectfully submits the following statement for the record to the Senate Health, Education, Labor, and Pensions Committee hearing on Securing the Pharmaceutical Supply Chain.

As the national professional association representing over 35,000 pharmacists who practice in hospitals and health systems, ASHP can offer unique and vital feedback on this important health care issue. Pharmacists in hospitals and health systems are experts in medication use who serve on interdisciplinary patient-care teams. They work with physicians, nurses, and other health care professionals to ensure that medicines are used safely, effectively, and in a cost-conscious manner. For more than 60 years, ASHP has helped pharmacists who practice in hospitals and health systems improve medication use and enhance patient outcomes. This includes working with patients to help them access the medications they need and to use them safely and effectively.

Pharmacists are the frontline caregivers in our medication use system. Given the number and complexity of medications administered to patients today, it is critical that our pharmaceutical supply chain be secure and consistent. As manufacturing of pharmaceuticals becomes more global in scope, we must ensure that products and raw materials are pure and unadulterated. ASHP has adopted policies (attached) dealing with supply chain integrity and FDA's authority on recalls. Furthermore, as demand increases for life saving medications and manufacturing processes become larger and more complex, we must ensure that capacity exists to provide adequate supplies of medications, especially those critical to patient care. For the last 10 years, ASHP has been tracking shortages of prescription medications and a disturbing trend has emerged. Since 2006, the number of drug shortages has nearly tripled, with no end in sight. In 2010 alone, there were 211 drug shortages, and that trend is expected to continue in 2011 as the number has already reached 200 shortages and may well exceed the 2010 number. While the causes of drug shortages are multifactorial, the quality and integrity of foreign ingredients and manufacturing have been a contributing factor. The attached policy on drug shortages was adopted in June by ASHP's House of Delegates. ASHP is committed to working with Congress, FDA and other supply chain members to address and hopefully reverse this alarming trend.

DRUG SHORTAGES

Shortages of prescription drugs in the United States have gained increasing attention in recent years due to the scope and severity of the drugs in short supply. The majority of these shortages occur in drugs that are generic injectables, often administered in a hospital or clinic setting. The shortages have been occurring for anticancer drugs, anesthetics, pain, and nutritional drugs, all of which play crucial roles in the care of patients. The result of drug shortages is that caregivers must scramble to find the drug, or use an alternative if one is available. Many caregivers have expressed concern that even if a therapeutic alternative exists, it is likely an older drug which may have more severe side effects or negatively interact with other medications the patient is taking. Further, drug shortages have caused widespread fear among caregivers who are deeply concerned that care could be delayed, rationed, or is provided in a suboptimal manner to stretch doses and preserve scarce supplies.

According to a study conducted in partnership between ASHP and the University of Michigan Health System, labor costs associated with managing drug shortages have an estimated annual impact of $216 million nationally, and more than 90 percent of respondents agreed that drug shortages were associated with an increased burden and increased costs today compared to 2 years ago.

Causes of drug shortages are many and complex. Manufacturing issues that lead to drug shortages include product quality issues that result in production halts or recalls, product discontinuations, and unavailability of active pharmaceutical ingredients (APIs) or other raw materials. Secondary shortages—or shortages that occur based on shifts in market demand caused by an initial shortage of another drug—are also common. Other contributing causes to drug shortages include quality issues that arise from the ever-increasing reliance on foreign ingredient and manufacturing sources and a lack of FDA resources to expedite approval of supplemental new drug applications and conduct foreign inspections. While not a cause of drug shortages, just-in-time inventory practices by product distributors and practice sites have removed the buffer previously provided by larger inventories and resulted in an immediate impact of drug shortages on patient care.

While information on the root cause of each drug shortage is not always publicly available, the cause of most shortages can be traced back to aspects of the manufac-

turing process. These manufacturing issues are compounded by substantial industry consolidation over the last few years that has resulted in fewer manufacturers producing critical drugs. When one manufacturer experiences a production interruption, other companies must ramp up production of their product to meet market needs. This increased production is sometimes, but not always, possible. In the case of sole-source drugs, this situation almost instantly results in a shortage situation.

ASHP continues to work with FDA, other health care provider groups and members of the supply chain to address the issue. However, we also believe Congress can help us as well. ASHP supports bipartisan legislation (S. 296, H.R. 2245) that would require drug manufacturers to notify the Agency when they experience an interruption in the production of a drug product potentially resulting in a shortage situation. According to FDA, in 2010 the Agency was able to avoid 38 drug shortages when they were made aware of production interruptions ahead of time. However, we believe other steps can be taken as well, for example, require confidential notification of the disruption in supply of single source active pharmaceutical ingredients (API), require manufacturers to develop continuity of supply plans, establish incentives for manufacturers to remain or re-enter the market, and urge FDA to develop expedited approval pathways for pre-1938 (unapproved) drugs. Finally, ASHP believes that FDA must have adequate resources devoted to alleviating and preventing drug shortages.

NOTIFICATION SYSTEM

Under current law, manufacturers are not required to report to FDA when they experience an interruption in the production of their products, unless that drug is deemed medically necessary by the agency. The same holds true for manufacturer plans to discontinue a product. Even in cases where the drug is deemed medically necessary and reporting is required, FDA has no enforcement mechanism to penalize a drug maker for failing to report these problems. This information could be extremely useful to FDA in the case of drugs with multiple suppliers where the agency could urge alternate suppliers to step up production of a product to offset the decrease in supply due to the interruption or discontinuation of the initial product. In some instances, FDA is not told there is a problem, or the nature of the problem. This information could be useful in determining the duration and severity of the interruption and may allow the agency to implement countermeasures to help ensure supply. By FDA's own account, in 2010 the agency was able to avoid 38 drug shortages when this type of notification was made available.

The importance of notification is highlighted by quality concerns associated with the increased globalization of pharmaceutical manufacturing. A number of drug shortages can be traced back to quality concerns with foreign-produced APIs. An extreme example was the heparin contamination that occurred in 2007, which resulted in a recall, and subsequent product shortage that was immediate and continued for an extended duration of time. While FDA has increased foreign inspections, it still lacks the resources necessary to fully address this issue. Therefore, drug shortages precipitated by recalls caused by substandard APIs will continue and likely increase.

Legislation (S. 296/H.R. 2245) in Congress would mandate that companies notify FDA of the interruption in production of any product 6 months in advance, or as soon as possible in the event of an unplanned stoppage. Manufacturers that fail to report this information would be subject to civil monetary penalties. This early warning system would allow the agency to communicate more effectively with manufacturers and others in the supply chain to plan for pending supply interruption. The early warning system should be the cornerstone of congressional action to address drug shortages.

CONFIDENTIAL NOTIFICATION FOR SINGLE-SOURCE API

In addition, information that can make drugs vulnerable to shortages, such as a single API source, is also frequently unknown beyond the manufacturer. This information is, and should be considered proprietary, but this lack of transparency hinders the development of contingency plans for vulnerable drugs. A requirement that manufacturers notify FDA when there is a single source of API may help the Agency work with manufacturers to identify backup sources should supply issues arise.

CONTINUITY OF SUPPLY PLANS

Related to the reporting or an early warning system, FDA could work with manufacturers to develop continuity of supply plans. The current lack of transparency acts as a significant barrier to this type of collaboration. With increased information exchange, contingency plans could be developed that include countermeasures such

as manufacturing redundancies or backup supplies; more effective communication among FDA, manufacturers and others in the supply chain; and finally, development of plans that utilize production capabilities of other manufacturers either here in the United States or abroad to ensure availability of a drug in short supply.

In 2010, FDA worked with APP Pharmaceuticals to help alleviate a shortage of propofol, a widely used anesthetic preferred by anesthesiologists because of its excellent safety profile compared to other available drugs. By enabling the company to work with its German counterpart to import the drug, FDA was able to substantially improve product availability after the shortage occurred. Using this example, if an acceptable foreign alternative could be identified before a shortage occurs through establishment of continuity of supply plans for vulnerable drugs, then importation could be expedited and the negative impact of a specific shortage on patient care could be minimized or averted. Importation represents an extreme example of contingency planning. In its simplest form, manufacturing strategies that include collaborating with other manufacturers, establishing back-up suppliers of raw materials and APIs, and creating alternative production capabilities that can be used as countermeasures would be a significant step forward to combating drug shortages. Contingency planning by companies producing drugs critical to patient care must be a standard of practice. S. 296/H.R. 2245 support the development of contingency plans for drugs that are vulnerable to shortages.

INCENTIVES

Further, shortages are occurring overwhelmingly among generic injectable drugs, where production processes tend to be more complex than their solid dosage counterparts. Low margins for these expired patent products coupled with complex manufacturing processes may lead some manufacturers to abandon production of these drugs altogether in favor of products with higher profit margins, thus reducing the number of potential suppliers of products critical to patient care. A way to offset this problem may be to explore incentives to encourage manufacturers to either stay in the market or enter the market with a new product line. There are several ways this could potentially be accomplished: (1) explore tax incentives for manufacturers to produce a drug in short supply or one deemed "vulnerable" to a shortage; (2) grant temporary exclusivity for a new product line of a drug in shortage or deemed "vulnerable" to one; (3) if a generic user fee program is created within the next reauthorization of the Prescription Drug User Fee Act (PDUFA), FDA could explore reduced user fees for drugs in short supply or deemed "vulnerable."

REQUIRE DEVELOPMENT OF AN EXPEDITED APPROVAL PATHWAY FOR PRE-1938 DRUGS

FDA must find a way to abbreviate and prioritize approval processes for existing therapies that are unapproved, but widely used and essential for patient care. For these drugs, the agency should work with manufacturers to fast track their approval for the U.S. market, especially in cases where the potential exists for those drugs to fall in short supply. Barriers to manufacturing and marketing these drugs must be minimized in order to foster production and availability of these drugs.

CONCLUSION

Unfortunately, there is no single solution that can prevent the occurrence of all drug shortages. The complexity of manufacturing processes, the requirement for safe and high-quality products, and globalization of the pharmaceutical supply chain all contribute to fluctuating product supplies that may never be entirely eliminated. However, there are critical steps that Congress, FDA and other stakeholders can implement to ensure that patient care remains available and safe. While the adjustments and compromises required from all stakeholders are difficult, the need for change is critical. First and foremost is the need for increased communication and transparency.

ASHP, along with several other stakeholder groups has been working collaboratively with Congress and supply chain stakeholders to develop solutions to the drug shortage problem. As indicated before, there is legislation in both houses of Congress as well as broad bipartisan support in the Senate for action. Passage of legislation that provides additional authority to FDA is a step in the right direction. In the long term, FDA will require additional resources to best address this and other issues that impact the quality and safety of drugs.

Attachment

ASHP POLICY POSITION 0907—PHARMACEUTICAL PRODUCT AND SUPPLY CHAIN INTEGRITY

Source: Council on Public Policy

To encourage the Food and Drug Administration (FDA) and relevant State authorities to take the steps necessary to ensure that (1) all drug products entering the supply chain are thoroughly inspected and tested to establish that they have not been adulterated or misbranded and (2) patients will not receive improperly labeled and packaged, deteriorated, outdated, counterfeit, adulterated, or unapproved drug products; further,

To encourage FDA and relevant State authorities to develop and implement regulations to (1) restrict or prohibit licensed drug distributors (drug wholesalers, repackagers, and manufacturers) from purchasing legend drugs from unlicensed entities and (2) ensure accurate documentation at any point in the distribution chain of the original source of drug products and chain of custody from the manufacturer to the pharmacy; further,

To advocate the establishment of meaningful penalties for companies that violate current good manufacturing practices (cGMPs) intended to ensure the quality, identity, strength, and purity of their marketed drug product(s) and raw materials; further,

To urge Congress and State legislatures to provide adequate funding, or authority to impose user fees, to accomplish these objectives.

This policy supersedes ASHP policy 0722.

ASHP POLICY POSITION 1003—FDA AUTHORITY ON RECALLS

Source: Council on Public Policy

To strongly encourage the Food and Drug Administration (FDA) to develop a standard recall notification process and format to be used by all manufacturers to facilitate the timely removal of recalled drugs; further,

To advocate that such notification should (1) come from a single source, (2) clearly identify the recalled product, (3) explain why the product is being recalled, (4) provide a way to report having the recalled product, (5) give instructions on what to do with the recalled product, and (6) be provided concurrently to all entities in the supply chain; further,

To advocate that the FDA be given the authority to order mandatory recalls of medications; further,

To urge the FDA to require drug manufacturers and the computer software industry to provide bar codes and data fields for lot number, expiration date, and other necessary and appropriate information on all medication packaging, including unit dose, unit-of-use, and injectable drug packaging, in order to facilitate compliance with recalls or withdrawals and to prevent the administration of recalled products to patients; further,

To urge the FDA to encourage postmarketing reporting of adverse events and product quality issues to enhance the recall system.

ASHP POLICY POSITION 1118—DRUG PRODUCT SHORTAGES

Source: Council on Public Policy

To advocate that the Food and Drug Administration (FDA) have the authority to require manufacturers to report drug product shortages and the reason(s) for the shortage, and to make that information available to the public; further,

To strongly encourage the FDA to consider, in its definition of "medically necessary" drug products, the patient safety risks created by use of alternate drug products during a shortage; further,

To support government-sponsored incentives for manufacturers to maintain an adequate supply of medically necessary drug products; further,

To advocate laws and regulations that would (1) require pharmaceutical manufacturers to notify the appropriate government body at least 12 months in advance of voluntarily discontinuing a drug product, (2) provide effective sanctions for manufacturers that do not comply with this mandate, and (3) require prompt public disclosure of a notification to voluntarily discontinue a drug product; further,

To encourage the appropriate government body to seek the cooperation of manufacturers in maintaining the supply of a drug product after being informed of a voluntary decision to discontinue that product.

This policy supersedes ASHP policy 0319.

PREPARED STATEMENT OF THE NATIONAL COMMUNITY PHARMACISTS ASSOCIATION (NCPA)

Dear Chairman Harkin, Ranking Member Enzi and members of the committee, NCPA welcomes this opportunity to provide input and suggestions to the committee regarding the pressing issue of securing the pharmaceutical supply chain. The National Community Pharmacists Association (NCPA) represents America's community pharmacists, including the owners of more than 23,000 community pharmacies, pharmacy franchises and chains. Together, these small business entities employ over 300,000 full-time employees and dispense nearly half of the Nation's retail prescription medicines.

Although we believe that the pharmaceutical supply chain in the United States is largely safe and secure, there are a number of different approaches or tactics that could be employed to provide further confirmation of integrity. One approach would be increased oversight or security measures to deter pharmaceutical cargo theft. NCPA is encouraged to note that Federal legislation has been introduced by Senator Charles Schumer, S. 1002, the Safe Doses Act, that would expand the penalties for pharmaceutical cargo theft. Implementing a track-and-trace system for pharmaceuticals is also a concept that has been discussed. NCPA continues to feel that track-and-trace technologies still remain largely unproven and potentially economically infeasible for the independent community pharmacy industry at this time. Given our position in the pharmaceutical supply chain and as health care providers, we want to share with you our ideas to further secure the supply chain.

NATIONAL, UNIFORM FEDERAL LICENSE STANDARDS FOR WHOLESALE DISTRIBUTORS AND LOGISTICS PROVIDERS

As part of any track-and-trace system or perhaps as a stand-alone program, NCPA recommends that the U.S. Government set national, uniform Federal license standards for wholesale distributors and logistics providers (3PLs). At the present time, wholesale distributors are licensed at the State level, which has resulted in a patchwork of conflicting requirements of varying rigor. By setting a high bar for wholesale distributors nationwide, the Federal Government could further safeguard the supply chain by making sure that only appropriately credentialed and legitimate entities are able to participate in the drug distribution aspect of the pharmaceutical supply chain. This new Federal standard would pre-empt the existing State requirements although the individual States could still certify compliance with the Federal standards and could register Federal licenses for an appropriate fee.

POSSIBLE RISK-BASED APPROACH/INITIAL IMPLEMENTATION ONLY DOWN TO WHOLESALER LEVEL

NCPA recommends that if a track-and-trace system were to be required for the U.S. pharmaceutical supply chain, Federal policymakers may wish to consider utilizing a risk-based approach to determine the scope of products to be included in any track-and-trace system, at least at the outset of any program. Possible approaches that could be utilized could focus efforts on certain controlled substances or pharmaceuticals that are high dollar/high volume products. Also in this way, the system could be tested and further refined prior to the possible expansion to other products as well. Another incremental approach that would ease the burden on the entire supply chain would be to have any track-and-trace system initially applicable only down to the wholesaler level. Wholesalers would have the necessary product information and would be able to track what products were delivered to each pharmacy. There are only a few thousand wholesalers compared to over 60,000 retail pharmacies.

INCENTIVIZE ADOPTION

In order to incentivize the voluntary adoption of track-and-trace technology, and if such a system were to be mandated for all participants, NCPA contends that Federal grants must be made available to smaller supply chain participants—like independent pharmacies—so that these small businesses are able to implement and maintain track-and-trace systems. In 2008, Accenture conducted a study that estimated the first year start up costs to implement a track-and-trace system would total approximately $110K per pharmacy.

Some of the participants in the February 2011 FDA public workshop, *Determining the System Attributes for the Tracking and Tracing of Prescription Drugs*, cited the fact that a number of supply chain participants should be able to realize several

value-added features of a track-and-trace system in terms of financial and brand protection benefit or in terms of potential theft reduction and inventory optimization. It should be noted that any operational benefits from track-and-trace systems may not be evenly distributed among larger multi-unit corporations and small businesses. Larger corporate entities involved in the supply chain—namely manufacturers, wholesalers and chain pharmacies—would likely realize value-added benefits that a track-and-trace system could bring to their overall business practices. However, for the majority of independent pharmacy owners, the cost of implementing a track-and-trace system would likely exceed any possible ancillary benefits like inventory management or theft reduction.

INTEROPERABILITY

Ensuring interoperability between the systems used by all participants in the supply chain is essential to the success of any track-and-trace program. Use of the standardized numerical identifier should avert some of the problems or inevitable snags that may occur when attempting to connect or ensure communication between varying manufacturers and distributors. Although the creation of a standardized numerical identifier should assist in paving the way for interoperability, much work remains to be done.

NCPA has concerns that at the beginning or advent of any track-and-trace program, pharmacies may be forced to use more than one set of technologies (hardware/software) in order to comply. This would inevitably add to the financial burden with which many independent pharmacies will be dealing. Some FDA workshop participants pointed out that in other industries, interoperability has only been realized when dealt with through government regulation—and NCPA feels that there may be some validity to considering this option in this instance.

It has been noted or suggested that some of the smaller supply chain participants may be able to rely on the systems or track-and-trace solutions of the larger participants. The most-likely scenario may entail an independent pharmacy relying on the track-and-trace system and network capabilities of their wholesale distributor. It is important to note that the cost to the pharmacy could vary greatly based on such an arrangement. Questions related to ownership of a pharmacy's data generated by the operation of the track-and-trace system would invariably arise. Additionally, this situation could become complicated in situations in which a pharmacy may need to switch their wholesaler for any reason. In order for this type of arrangement to be mutually beneficial to both wholesaler and pharmacy, more detailed discussions as to the roles and responsibilities of both parties would need to be discussed in greater detail.

AUTHENTICATION

NCPA would like to point out that there must be consensus around the definition of authentication—and at which point in the supply chain such authentication should occur. In the past, many participants in the supply chain have raised the issue of the inherent distinction between track and trace. In order to track, supply chain participant would only need verification that the serialized number is indeed valid. In order to trace, a supply chain participant would need to be able to actually access and verify all of the prior transactions.

If it were determined that all supply chain participants must do both—track and trace—pharmacies, which serve as the last stop in the supply chain, would have a potentially greater burden than other supply chain participants if they were required to actually authenticate or trace the entire distribution history of each product. Several workshop participants raised the point that perhaps only certain products or classes of products with the greatest risk of being counterfeited should be subject to tracing requirements. Also, other participants suggested that FDA or regulators would be the only entities that would have an actual need for a full distribution history. If access to the entire distribution history were limited to FDA or other regulators, this may also alleviate some of the concern expressed by a number of entities who are understandably concerned about supply chain partners having access to their proprietary data.

Another issue that would need to be determined with regard to authentication would be standard operating procedures that would be employed in the event that a product could not be authenticated. NCPA questions which participant (sender, recipient or system) would have to ultimately bear the cost of the product in the event a product could not be authenticated and then subsequently sold. Pharmacies would need to know whether they could return such products back to upstream trading partners or if they would be forced to assume the cost of such unsalable items. Also, there needs to be clear protocol surrounding the reporting of such an event.

INFERENCE

Inference is one facet of the track-and-trace process that would greatly ease the time and labor costs for distributors and chain pharmacies but would not necessarily be available for independent pharmacies. Inference allows distributors to read a case or pallet of product and then infer that a certain set of serial numbers exists within that case or pallet. This same process could easily be employed by the chain pharmacy corporations that receive products from the manufacturer at a chain pharmacy warehouse. However, independent pharmacies typically do not receive products in case or pallet form from a dedicated warehouse and, therefore, could be forced to individually or manually scan each bottle or serial number as it arrives in the pharmacy. This would be extremely time consuming and would necessitate an increase in labor costs for independent pharmacy owners. NCPA recommends that as part of any discussions surrounding a proposed track-and-trace system, efforts to pilot inference at the tote level must be considered.

NCPA strongly recommends pilot projects be pursued for any track-and-trace system in order to adequately identify and work through the complexities and substantial costs surrounding such a system, and that all supply chain participants be involved in any proposed pilot program.

CONCLUSION

NCPA appreciates the opportunity to submit these comments as the committee discusses the issue of securing the pharmaceutical supply chain. The committee may wish to examine a variety of approaches to this multi-faceted issue including efforts to deter pharmaceutical cargo theft, implementing national uniform Federal licensure standards for wholesale distributors and potentially the use of some form of track and trace technology for pharmaceuticals. Thank you for your consideration.

DEPARTMENT OF HEALTH & HUMAN SERVICES,
FOOD AND DRUG ADMINISTRATION,
SILVER SPRING, MD 20993,
February 9, 2012.

Hon. TOM HARKIN, *Chairman,*
Committee on Health, Education, Labor, and Pensions,
U.S. Senate,
Washington, DC 20510.

DEAR MR. CHAIRMAN: Thank you for providing the opportunity for the Food and Drug Administration (FDA or the Agency) to testify at the September 14, 2011, hearing before the Committee on Health, Education, Labor, and Pensions entitled "Securing the Pharmaceutical Supply Chain." This letter provides responses for the record to questions posed by certain members of the committee.

If you have further questions, please let us know.

Sincerely.

MICHELE MITUL FOR JEANNE IRELAND,
Assistant Commissioner for Legislation.

RESPONSE OF THE FOOD AND DRUG ADMINISTRATION TO QUESTIONS OF SENATOR BENNET, SENATOR ROBERTS, AND SENATOR KIRK

SENATOR BENNET

Question 1. The Institute for Safe Medication practices found in a survey of 1,800 health care practitioners that 52 percent of hospitals and pharmacists in the survey reported using "gray market" suppliers in order to secure medicines during a time of drug shortage. Do you think that a system that enables FDA to know where drugs are in the distribution chain could be helpful in addressing this challenge?

Answer 1. The gray market that emerges when drug shortages occur takes advantage of the vulnerability of health care institutions and pharmacies that are desperately seeking to fill the voids left by drug shortages. A robust track-and-trace system will help protect consumers from threats posed by illegal or substandard products, which may result from a drug shortage situation, in addition to providing accountability and transparency within the supply chain. A track-and-trace or uniform pedigree system will not solve the shortage, but it can help provide assurances that a drug being offered for sale is from the legitimate supply chain and is authentic.

Particularly helpful to ward against gray market products arising in drug shortage situations would be an expansion of existing law, which requires sole manufacturers to notify FDA of a discontinuance of certain drug products. The Administration has endorsed legislation that would require all manufacturers to provide notice to FDA of any issue that may lead to a disruption in supply of a drug product and that would provide explicit authority to enforce such reporting through civil money penalties. Expansion of the current notification provision would help FDA prevent drug shortages and be on the lookout for counterfeit products that arise in shortage situations. Moreover, the addition of enforcement authority and penalty provisions would enable FDA to ensure that it receives timely information related to potential drug shortages and would serve as a strong incentive for manufacturers to comply.

Question 2. Does FDA receive information at the border when drugs come in through United States' land or sea ports about whether a drug is FDA compliant? And if the drug appears tainted or physically damaged, what options does FDA have to destroy the product? How does this compare to the system that other countries have in place?

Answer 2. Currently, FDA is only authorized to refuse admission of drugs that appear to be adulterated, misbranded, or unapproved. Unlike with foods, FDA is not currently authorized to require the submission of drug information as a condition of entry or refuse admission based solely on the failure of an importer to provide the required information. Clear authority to require information, and to refuse admission if such information is not provided, would improve FDA's ability to monitor imported products for compliance with applicable laws. The success of FDA's electronic review system is linked to the quality of data that importers and entry filers submit for the entry of their products. This information would not only enable FDA to better target higher-risk products, it would also minimize delays by allowing for increased use of electronic screening.

Currently FDA only has the authority to issue a "notice of refusal of admission" for noncompliant, drug-related imports. Upon issuance of the "notice of refusal of admission," FDA must turn over authority to the U.S. Customs and Border Protection (CBP), which may require either exportation or destruction of the non-compliant import under the Tariff Act, 19 U.S.C. 1595. Currently, FDA needs to seek Department of Justice (DOJ) support for seeking a seizure of packages of low or no-declared value, and packages without return addresses, or packages that were returned and simply rerouted to the United States. FDA supports allowing CBP to destroy products in violation of FDA regulations that are valued at $2,000 or less or that pose a reasonable probability of causing a significant adverse health effect, with an opportunity for a hearing to be held after destruction in order to (1) avoid the re-introduction of violative products; (2) lessen the Agency's burden and expenditure on low-value, highly unsafe products; (3) decrease the number of intentionally misdeclared low-value shipments avoiding commercial shipper oversight. Absent these authorities, FDA is often forced to store, or when there is a return address return, violative products to their senders because the current process for destruction requires a hearing, which is time-consuming and costly. Such violative drugs can find their way back to U.S. ports of entry several times, posing a potential threat to consumers and wasting critical resources that could be better spent identifying new threats. This ineffective process produces a revolving door for violative drugs.

In January 2011, FDA collected information about various aspects of drug safety from regulatory authorities in Australia, Canada, India, Israel, Japan, New Zealand, the People's Republic of China, South Africa, Switzerland, and the European Medicines Agency. In response to questions about whether the regulatory authorities require documentation for the admissibility of imported pharmaceuticals, and whether they have the ability to prohibit the importation of pharmaceuticals, the Agency received a variety of answers. Generally, all had requirements for documentation as a condition of entry, with the exception of the European Medicines Agency, because it is a review authority and regulatory compliance is left to the European Member States. For example, Australia requires that imported drugs have to be on the Australian Register of Therapeutic Goods. By contrast, Health Canada inspectors and Canadian Border Services officers can require persons who import a pharmaceutical product to provide sufficient evidence to show that the drugs are being imported in compliance with the Food and Drugs Act and its Regulations, and other relevant legislation, such as the Controlled Drugs and Substances Act.

Question 3. GAO has been critical of FDA having some inaccurate and duplicate information in its databases. FDA has proposed having a unique identifier for all establishments that are importing drugs into the United States. It is my under-

standing that Customs and Border Protection control the implementation of this unique identifier. Would giving FDA this authority to implement a unique identifier for establishments help FDA get rid of some of this inaccurate data? What will happen going forward if FDA continues not to have this authority?

Answer 3. FDA strongly supports having a unique facility identifier (UFI), such as a Dun and Bradsheet D-U-N-S number, associated with each facility and supports a statutory requirement requiring submission of a UFI as a condition of registration and as a condition of import, for several reasons. First to be aware of entities in the global supply chain and to conduct appropriate inspections, FDA depends upon a number of electronic systems. Some of the databases upon which FDA relies include: Field Accomplishments and Compliance Tracking System or FACTS (inspection tracking database), Document Archiving, Reporting and Regulatory Tracking System or DARRTS (applications database), Establishment Evaluation System or EES (application inspection database), and Operational and Administrative System for Import Support or OASIS (imports database).[1] Currently, establishments may be identified by different names and addresses in different systems. Requiring establishments to provide UFIs during the registration and importation processes will enable FDA to more easily cross-reference information about the establishments and their products in these various databases. In addition, if FDA is authorized to require submission of a UFI, and chooses to use an existing external identifier system such as D-U-N-S, it can leverage private data sources or data from other countries that already make use of these identifiers to help cross-check its data.

Second, to be aware of entities in the global supply chain and conduct appropriate inspections, FDA also has to be able to distinguish between different facilities that are often easily confused. UFIs play an important role in FDA being able to do so in a timely manner. One typical scenario in which UFIs are critical to FDA is when the Agency identifies a facility in China that it believes requires inspection. Many Chinese facilities have names that are difficult to differentiate in FDA databases, in part because it is common in China for the name of the facility to begin with the name of the city in which the facility is located. Having UFIs associated with such establishments enables FDA to more easily distinguish among them.

Third, existing Facility Establishment Identifiers (FEIs) have not been effective. In addition to recommending the submission of D-U-N-S Numbers, for many years FDA also has been assigning FEI numbers. However, as with D-U-N-S Numbers, there is no requirement that these numbers be submitted to FDA, and the Agency has been generating them on its own. This has led to a situation where multiple FEI numbers may have been assigned to a single establishment. This situation has created confusion both within FDA and industry.

Giving FDA the authority to require submission of true, independent, and interoperable UFIs at registration and importation would help ensure the accuracy of our databases and better enable FDA to ensure proper import targeting and enforcement of our import alerts. This authority also better enables FDA to prevent potentially unsafe products from entering U.S. commerce.

Specifically regarding UFIs and importation, CPB collaborates and enforces laws associated with multiple U.S. government agencies and, therefore, would presumably want to seek uniform agreement among the stakeholder agencies regarding what the UFI should be. CBP currently requires a Manufacture Identification (MID) number, but that is not a true, independent, interoperative UFI. If the MID number is entered incorrectly, the system will create a new FEI number in FDA's database, thereby associating multiple FEB and MID numbers to, in actuality, one specific firm. This process has led to FDA's databases containing inaccurate information, as noted by the Government Accountability Office (GAO).

Currently, FDA does not have explicit statutory authority to require the submission of UFIs. In May 2009, FDA issued guidance requesting that establishment owners and operators submit D-U-N-S Numbers. Some registrants are providing this information, but not all. For those who do not comply with FDA's request, the Agency seeks to obtain the number on its own. However, this process imposes a burden to FDA, and we are not always successful in obtaining the correct number. Absent explicit statutory authority to require UFIs, the Agency cannot obtain the information it needs to make its databases fully operational.

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[1] These databases were not developed to be compatible with one another and, initially, had functions that were completely separate. After years in operation, it is now apparent that the ability of these databases to interface and share information with one another would be very useful. Unfortunately, it is nearly impossible to retrofit systems like these to make them compatible. The best way to make them interface is by establishing some shared data standards, like UFI.

Question 4. Ms. Autor explained in her testimony that in many other countries the burden of proof is on the companies to prove that their drug is compliant with the regulatory standard of the country they are trying to enter. She noted that in the United States the opposite is the case—the burden of proof is on the FDA to prove that a drug is not compliant. Can FDA point to other countries that they are aware of that place the burden of proof on the manufacturer?

Ms. Autor's testimony was in the context of "Securing the Pharmaceutical Supply Chain" and, specifically, requesting a certification or other assurance of compliance with applicable standards or requirements as a condition of importation. Ms. Autor said in part that other countries place the burden on the importer or product owner to prove that its drug is compliant with country requirements. In the United States, FDA has the burden of showing an "appearance" of a violation to detain and refuse an imported product.

Most countries require drug manufacturing sites to be licensed before product can be distributed in their countries. Canadian and European Union (EU) regulators, for example, issue an establishment (or site) license only after a Current Good Manufacturing Practice (CGMP) inspection finds the establishment compliant. Under the Federal Food, Drug, and Cosmetic Act (FD&C Act or the Act), drugs that are subject to premarket approval must pass a CGMP inspection to be approved. However, many over-the-counter (OTC) drugs sold in the United States are marketed under the OTC monograph system, rather than under individual approved product applications, and therefore, are not subject to CGMP inspection prior to distribution under this authority. For these OTC monograph drugs, there is no other provision in the Act requiring a passing CGMP inspection prior to distribution. Unlike the Canadian and EU establishment or site licensure requirements described above, the establishment registration provisions of section 510 of the FD&C Act do not require that a firm pass inspection before it is duly registered. Further, because section 510 of the FD&C Act requires only that an establishment's owner/operator "immediately register" the establishment upon commencing manufacturing (see 510(c) and (i)), even upon receipt of a new registration, it will take FDA some time to conduct an inspection.

As noted above, other countries can require persons who import a pharmaceutical product to provide sufficient evidence to show that the drugs are being imported in compliance with their drug laws. Because FDA may not have inspected a facility, or may not have inspected it recently, this kind of authority would be very useful.

Additionally, some countries, like the EU Member States, also have a batch recontrol provision, requiring batch retesting before entry is permitted for certain countries of origin. FDA has no comparable requirement for most human drug products.

SENATOR ROBERTS

Question 1. I have been on record raising concerns with additional government regulations in a time when companies and individuals are already overburdened with red tape. Some are suggesting that a sweeping statutory change is needed to promote safety and jobs. I am skeptical of this opinion. So instead I'll ask, what improvements to the upstream supply chain integrity, and addressing the problems therein, are currently within FDA authority and how are you utilizing these current authorities to better ensure safety and effectiveness of drugs for American consumers?

Answer 1. FDA has undertaken a wide range of activities aimed at addressing the challenges of globalization. The rapidly changing global environment, and a desire to move from a posture of intercepting harmful products to anticipating and preventing the arrival of such goods, has prompted FDA leadership to develop a strategy for addressing the challenges of globalization entitled "Pathway to Global Product Safety and Quality." To achieve this transformation, FDA is developing an international operating model that relies on enhanced intelligence, information sharing, data-driven risk analytics, and the smart allocation of resources through partnerships.

The new approach rests on four core building blocks:

- FDA, in close partnership with its foreign counterparts, will assemble global coalitions of regulators dedicated to building and strengthening the product safety net around the world.
- With these coalitions, FDA intends to develop a global data information system and network in which regulators worldwide can regularly and proactively share real-time information and resources across markets.
- FDA will continue to expand its capabilities in intelligence gathering and use, with an increased focus on risk analytics and thoroughly modernized information technology (IT) capabilities.

• FDA will effectively allocate Agency resources based on risk, and leveraging the combined efforts of government, industry, and public- and private-sector third parties.

The essence of this strategy marries creative international coalitions with cutting-edge investigative tools to continue to provide the consistently high level of safety and quality assurance the public expects—and deserves. FDA will continue to partner with other Federal agencies, the States, and nations across the world. It will also look to Congress to modernize its antiquated authorities so that FDA's legal tools keep pace with globalization.

Question 2. I believe that the statute is silent on how often foreign drug establishments must be inspected, so I guess my question is, does FDA really need new authorities to inspect foreign facilities? Because there is a difference between a need and a want.

Answer 2. You are correct that the statute is silent on how often foreign drug establishments must be inspected. The statute does require that domestic drug inspections be inspected every 2 years. FDA does not need new authority to conduct foreign inspections, however, new authority would be required to change the biennial inspection requirement for domestic drug manufacturers to an inspectional frequency based on risk, regardless of facility location. Such authority would ideally enable FDA to adjust inspection frequencies based on risk factors like the nature of the drug, the processing and control methods, and the availability of other credible information about the establishment from other reliable sources, including other governmental and non-governmental inspecting or auditing organizations, and to use its limited resources most effectively.

Question 3. The FDA committed to providing the committee with a full and complete list of all foreign drug establishments that are involved in the U.S. drug supply chain. Please provide that list.

Answer 3. FDA provided this information via e-mail to your staff on October 18, 2011.

Question 4a. Drug counterfeiting, theft and diversion are a serious public health issue and a bottom line issue for industry as well. Just last year stolen insulin managed to make its way back onto legitimate pharmacy shelves and reached patients. This is a heat-sensitive product that will not work if improperly stored. How was this deception possible? Right now there is no comprehensive national system to track and authenticate packages of drugs as they travel from the manufacturer to wholesaler to pharmacy.

Answer 4a. Stolen or diverted drugs are a public health concern for the very reason you have described, as we cannot be certain that these products have been stored or handled properly once they have left the legitimate supply chain. Loss of potency or integrity cannot necessarily be detected by physical examination with the naked eye, but may only be determined by laboratory analysis of potency and integrity. The lack of a comprehensive national system to track and authenticate packages of drugs as they travel from the manufacturer to wholesaler to pharmacy is the reason such diversion and reentry can occur.

Question 4b. What steps can the FDA take to help increase security and transparency of drug distribution?

Answer 4b. To further improve the security of the drug supply, FDA supports a comprehensive national track-and-trace system and continues its work to develop standards for identification, authentication, validation, and track and trace for prescription drugs, as directed by section 505D of the FD&C Act. A robust track-and-trace system will help protect consumers from threats posed by illegal or substandard products, in addition to providing accountability and transparency of the supply chain. An initial step of FDA's track-and-trace standards development included issuance of a final guidance to industry entitled *Guidance for Industry: Standards for Securing the Drug Supply Chain—Standardized Numerical Identification (SNI) for Prescription Drug Packages* (See March 29, 2010, *Federal Register* (75 FR 15440)), describing the Agency's recommendation for unique identification of prescription drugs at the package level. In addition, in February 2011, FDA held a public workshop, which explored approaches for achieving an effective and feasible track-and-trace system for finished prescription drug products. Comments from supply chain stakeholders are being considered as we develop the standards for the validation, authentication, and tracking and tracing of prescription drugs to enhance the security of the drug supply chain against counterfeit, diverted, and other substandard drugs.

Question 4c. Does the FDA need additional authorities or a statutory mandate to ensure drug traceability becomes a reality?

Answer 4c. We are working on developing standards for a national, interoperable track-and-trace system in the United States. However, even with standards developed, additional authority would be helpful to require a cost-effective track-and-trace system for all products throughout supply chain.

Question 5. What are the potential costs to individual pharmacies if we implement a full track-and-trace program?

Answer 5. Because the design of a track-and-trace system has not been determined by Congress, it is challenging to estimate the costs to individual pharmacies to implement; the cost would depend on the characteristics of the particular track-and-trace system that is eventually required; for example, limiting track-and-trace requirements to receipt by the pharmacy, rather than to the point of sale to the patient, would lower costs. We are sensitive to the costs that pharmacies might have to incur to implement and maintain such a system and are mindful of that as we develop the standards. Because track and trace is being done for products in other industries, the equipment and technology appears to be readily available and, therefore, the costs may have decreased since these reports were issued and continue to decrease as the technology advances and becomes more widely used.

SENATOR KIRK

Question 1a. Earlier this year, FDA asked for input from stakeholders on beneficial system attributes for the tracking and tracing of prescription drugs. But this is only a preliminary step. What is the current status of FDA's efforts to standardize tracking and tracing requirements for the pharmaceutical supply chain, and how will "promising technologies" be incorporated into the new standards?

Answer 1a. During FDA's February 2011 public workshop titled "Determination of System Attributes for the Tracking and Tracing of Prescription Drugs," approaches for achieving an effective and feasible track-and-trace system for finished prescription drugs were explored. Following the workshop, FDA published a *Federal Register* Notice and opened a public docket to solicit feedback from supply chain stakeholders. The comment period was extended to allow for stakeholders to consider the workshop summary. The comments have been reviewed and considered as we continue to develop the remaining standards for authentication, validation, and track and trace.

The Agency has reviewed and considered current and promising technologies as it develops these standards. Some technologies can be considered as on-product or standalone technologies that provide a method to identify or authenticate a product through visual assessment or specific analytical methods. These technologies can be applied directly on the package (i.e., holograms, tamper-evident packaging) or directly on or in the dosage form (i.e., nanotechnological component or chemical taggant). Other technologies to consider include those that can be used to enable identification, validation, authentication, and track and trace of prescription drugs, such as data carriers, scanners, serialization software, traceability software, data management software, and analytical software. The level of availability, adoption, and interoperability of each of these technologies is being considered as we develop the standards. The standards will likely entail several of these technologies to achieve an effective and feasible track-and-trace system for prescription drugs. However, as you note, industry will not be required to adopt FDA standards if the Agency is not given authority to do so.

Question 1b. In addition, has FDA done any benchmarking with other Federal agencies to ascertain how those agencies are dealing with comparable policy objectives? For example, though different in nature, the Department of Defense is engaged in evaluating and/or deploying a variety of initiatives and technologies related to the tracking and tracing of high priority, high security items similar in importance and sensitivity to the protection of the pharmaceutical supply chain. What initiatives and technologies being considered or deployed by other Federal agencies such as DOD are you evaluating and benchmarking relative to securing the Nation's pharmaceutical supply chain?

Answer 1b. Yes, FDA has done benchmarking with other Federal agencies, including the Department. of Defense, U.S. Postal Service, Federal Aviation Administration, and National Aeronautics and Space Administration, to learn about their systems and technologies used to conduct tracking and tracing of supplies, mail, airplane parts, or aerospace parts, respectively. While this benchmarking was useful, we learned that no single system, model, or technology currently employed could be applied directly to the track-and-trace system that the Agency envisions for pre-

scription drugs, in part due to differing supply chain and distribution models, and the entities involved. This benchmarking was conducted as part of our research to gain insight on technologies used or under consideration and systems or processes used to manage the tracking and tracing capability.

Question 2. For a prescription drug track-and-trace system to be efficient and effective, it should be electronic rather than paper-based. An electronic system can incorporate human-readable elements on labels or tags. With today's technology, a barcode—in particular, a 2-D bar code—can incorporate a great deal of information accurately and be read easily and inexpensively. RFID technology can capture even more information and be read even more easily, since the RFID tag does not need to be in the line of sight of the reader. Updated information can easily be added as prescription drugs move through the supply chain. Serialization software can uniquely identify individual packages or groups of packages (e.g., pallets).

Furthermore, an electronic system may benefit from the existing, internationally-recognized technical standards, such as those issued by GS1, to facilitate interoperability along supply chains that may extend beyond our borders. GS1 standards can also address FDA's stated concern regarding the absence of a system of unique drug facility identifiers. To what extent has FDA considered the use of a partial or end-to-end electronic track-and-trace system for prescription drugs, and will that system be compatible with, or conform to recognized international standards?

Answer 2. FDA agrees that a fully electronic track-and-trace system is desirable to allow for interoperability and efficiency in processing data exchange between all supply chain participants. FDA also encourages accountability and transparency of all supply chain participants to improve the security of the drug supply and level the responsibility across the supply chain. As noted above, various technologies are being considered as we develop the standards for validation, authentication, and tracking and tracing, and the standards will likely entail several technologies to achieve an effective and feasible track-and-trace system, for prescription drugs. At the February 2011 public workshop, FDA shared the following as potential attributes of a track-and-trace system also under consideration:

- Ability to capture the unique identification of a product and the status of the product.
- Ability to ensure interoperability to enable supply chain participants to securely capture, store, and exchange track-and-trace data accurately and efficiently.
- Ability to authenticate the unique identifier SNI and entire distribution history of each product.
- Ability to create an electronic pedigree at any point during the movement of the product through the supply chain.
- Ability to enable appropriate access to track-and-trace data necessary to achieve system goals.
- Ability to ensure security of data and systems from falsification, malicious attacks, and breaches.
- Ability to ensure confidential commercial information is protected.
- Ability to ensure that patient privacy is maintained.

While we are aware of track-and-trace models that include some and not all members of the supply chain, FDA believes these partial models leave potential vulnerabilities in the supply chain and do not provide sufficiently enhanced security. In addition, counterfeit or other substandard drugs can enter anywhere in the supply chain. For these reasons, FDA believes that all members of the supply chain need to be participating in the track-and-trace system.

FDA intends to harmonize its standards development with international consensus standards to the extent practicable, as we have done with our *Guidance for Industry for the Standardized Numerical Identification (SNI) for Prescription Drug Packages* (March 2010).

[Whereupon, at 12:07 p.m., the hearing was adjourned.]

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