Testimony Before the Senate Health, Education, Labor, and Pensions Committee
"Securing the Pharmaceutical Supply Chain"
Wednesday, September 14, 2011
10:00 a.m.
430 Dirksen Senate Office Building

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, California 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 US 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 U.S. and Western Europe.

Our consortium was incorporated in June of 2009 with 6 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 policy makers. 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 manufactures, 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 U.S. 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 U.S. but use an FDA registration to convey a sense of FDA approval to non US-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 two 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 U.S. 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 U.S., and that more than 80% of the drugs consumed in the U.S. are now manufactured outside the U.S.

  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.