

Report to Committee on Appropriations
Report on
FDA's Approach to Medical Product Supply Chain Safety

In Response to
The Joint Explanatory Statement to Accompany H.R. 1105
The Omnibus Appropriations Act, 2009

Department of Health and Human Services
Food and Drug Administration
July 2009

/s/
Joshua M. Sharfstein, M.D. for
Commissioner of Food and Drugs
July 14, 2009

This report entitled, FDA’s Approach to Medical Product Supply Chain Safety, is in response to the following language from the Joint Explanatory Statement to Accompany H.R.1105, The Omnibus Appropriations Act, 2009:

Similar to a recent approach FDA has taken to address overall food safety issues, FDA is directed to prepare and provide to the Committees on Appropriations a comprehensive approach to ensuring the safety of medical products from the manufacturing of raw ingredients or components to consumer use.

TABLE OF CONTENTS

INTRODUCTION	I
I. TRENDS AND CHALLENGES TO ENSURING SUPPLY CHAIN SAFETY	1
A. THE VOLUME OF IMPORTS AND THE NUMBER OF FOREIGN SITES ARE GROWING	1
B. CONSUMERS ARE USING MORE MEDICAL PRODUCTS	3
C. THERE ARE GREATER OPPORTUNITIES FOR ECONOMICALLY MOTIVATED ADULTERATION	3
II. TAKING A COMPREHENSIVE APPROACH TO SUPPLY CHAIN SAFETY	4
A. FOCUS ON PREVENTION	4
1. <i>Implement quality management systems.....</i>	<i>5</i>
2. <i>Increase harmonization.....</i>	<i>6</i>
3. <i>Strengthen beyond our borders initiative</i>	<i>7</i>
4. <i>Develop good importer practices (GIPs)</i>	<i>9</i>
5. <i>Establish systems to identify medical products</i>	<i>10</i>
B. ENHANCE REGULATORY INFORMATION	11
1. <i>Upgrading FDA information technology (IT) infrastructure</i>	<i>11</i>
2. <i>Harmonizing inventory.....</i>	<i>12</i>
3. <i>Improving the electronic registration and listing system</i>	<i>12</i>
4. <i>Expanding information sharing.....</i>	<i>13</i>
C. IMPROVE FDA’S SCIENTIFIC AND ANALYTIC CAPABILITIES	14
1. <i>Identifying and testing innovative uses of new technologies</i>	<i>14</i>
2. <i>Using and refining state-of-the-art risk management.....</i>	<i>15</i>
D. EXPAND RISK-BASED INSPECTION AND ENFORCEMENT	16
1. <i>Increasing FDA inspections</i>	<i>16</i>
2. <i>Increasing other methods of verification.....</i>	<i>17</i>
3. <i>Launched a secure supply chain (SSC) pilot</i>	<i>17</i>
4. <i>Achieving credible deterrence through increased enforcement</i>	<i>18</i>
III. OPPORTUNITIES FOR FY 2010	19
IV. CONCLUSION.....	19

INTRODUCTION

Globalization presents serious challenges to the ability of the U.S. medical product¹ safety system to protect American families. Among these challenges are the growth in the number of medical products produced abroad, the increasingly complex path that medical products travel from source materials to consumers, and the greater chance for the intentional substitution of ingredients for profit (economic adulteration).

FDA is implementing a comprehensive approach to medical product safety along the supply chain, similar to its approach to food safety. The ultimate goal of these efforts is to protect Americans from contamination, diversion, counterfeiting, and other risks that could harm patients. In FDA's fiscal year (FY) 2009 appropriation, Congress directed FDA "to prepare and provide to the Committees on Appropriations a comprehensive approach to ensuring the safety of medical products from the manufacturing of raw ingredients or components to consumer use." This report addresses that directive by focusing on supply chain safety.²

Supply chain safety refers to 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, importation, sale and distribution. Although FDA has a significant number of efforts under way that address medical product safety issues beyond the supply chain,³ addressing supply chain safety presents some of the greatest challenges.

¹ For the purposes of this report, *medical products* includes human drugs, biologics, and medical devices, but not special dietary products, medicated feeds, veterinary drugs or radiation-emitting products that are not otherwise medical devices.

² Other reports on medical product safety underscore the importance of FDA's supply chain safety efforts. In December 2007, FDA's Science Board Subcommittee on Science and Technology issued a report concluding that FDA was not positioned to meet the demands of its regulatory responsibilities in light of the challenges of regulating globalized industries and the need to manage new science and technologies. The 2007 report recommended FDA strengthen its collaboration with other government agencies as a way to improve medical product safety programs. A supplemental report, issued in May 2008 by the Science Board Subcommittee on the Office of Regulatory Affairs, contained similar findings and recommended that FDA conduct more domestic and foreign inspections, coupled with certification programs for foreign manufacturers, greater inspection by foreign regulatory authorities, and improved risk-management inspection procedures. FDA has incorporated these approaches into its supply chain safety initiative.

³ For recent FDA actions to improve medical product safety beyond the supply chain, we direct the committees to *Promoting and Protecting the Health of the Public*, FDA's Response to the Institute of Medicine's 2006 Report (<http://www.fda.gov/oc/reports/iom013007.pdf>). A follow-up report to Congress - *Drug Safety Response to the Institute of Medicine Report* will be available imminently.

This report identifies trends and challenges that FDA faces all along the supply chain. To address them and protect public health, FDA has adopted four primary strategies:

- focus on prevention
- enhance regulatory information
- improve FDA's scientific and analytic capabilities
- expand risk-based inspection and enforcement

This report describes these four strategies and the steps that FDA is taking to implement them.

I. TRENDS AND CHALLENGES TO ENSURING SUPPLY CHAIN SAFETY

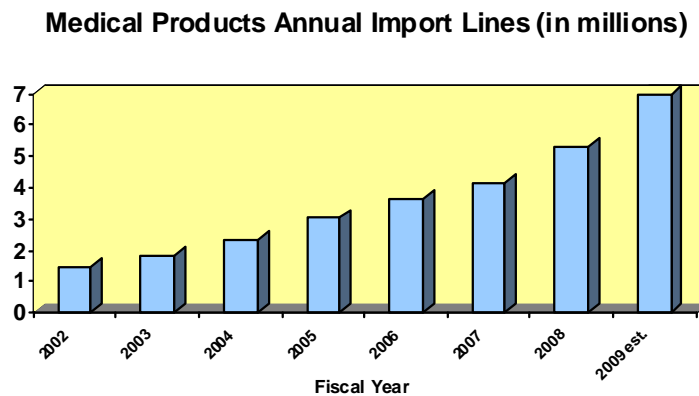
Several trends illustrate the challenges FDA faces to protect the medical product supply chain. These trends and challenges include:

- the expanding volume of imported medical products, ingredients, and components and the growth in the number of foreign manufacturing sites
- the increasing consumer use of medical products
- greater opportunities for economically motivated adulteration.

A. The Volume of Imports and the Number of Foreign Sites are Growing

The growth in imports during the past decade has been staggering. FDA processed approximately 5.3 million entry lines⁴ of medical products in FY 2008.⁵ This is an approximate 367 percent increase during the past seven years, with average annual growth of more than 25 percent per year during that period. This trend is expected to continue for the foreseeable future.

Figure 1:



There has also been tremendous growth in the number of foreign facilities manufacturing medical products. Figure 2 displays the growth in the number of drugs manufactured at foreign sites. Figure 3 depicts the growth in foreign medical device establishments.⁶

⁴ An import *entry line* refers to the portion of an import entry document (the document filed with the Bureau of Customs and Border Protection to secure the release of the imported product into U.S. commerce) that lists a separate item. Each item in the entry classified under a different tariff code must be listed separately.

⁵ Figure 1 includes approximately 1 million lines of “U.S. goods returned,” many of which were medical devices shipped as components to Mexico for assembly, then returned as finished products. Figure 1 also includes personal internet pharmacy shipments via courier. “U.S. goods returned” are products made in the U.S., exported to another country, then imported back into the United States. Combined, U.S. goods returned and internet pharmacy imports shipped via courier account for approximately half a million lines of the total 5.3 million reported.

⁶ Figures 2 and 3 actually underrepresent the increase in foreign facilities that have an impact on supply chain safety, as Figure 2 does not include the number of foreign excipient (inactive ingredient)

Figure 2:

**Number of Finished Drugs, Intermediates and APIs Manufactured at Foreign Sites
(by Registered Sites)**

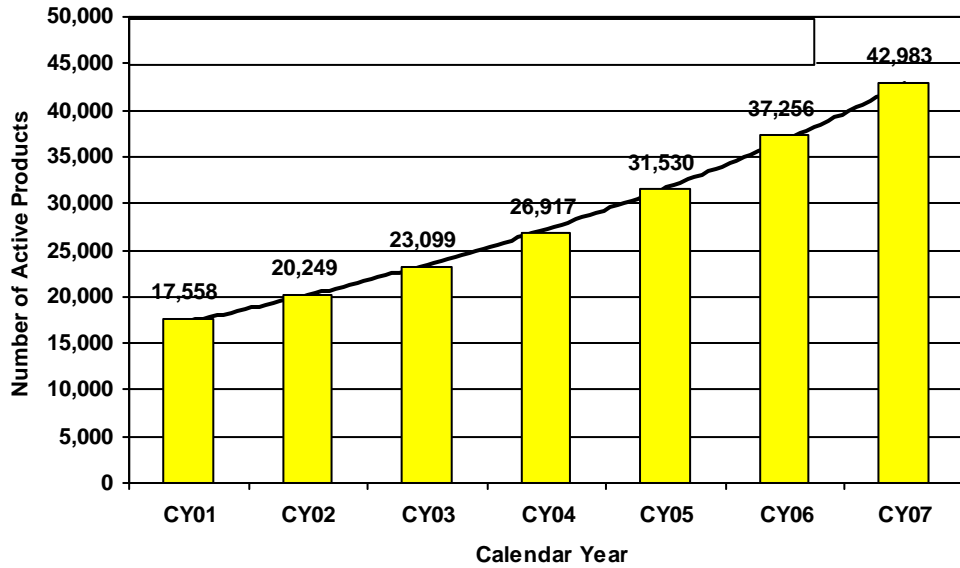
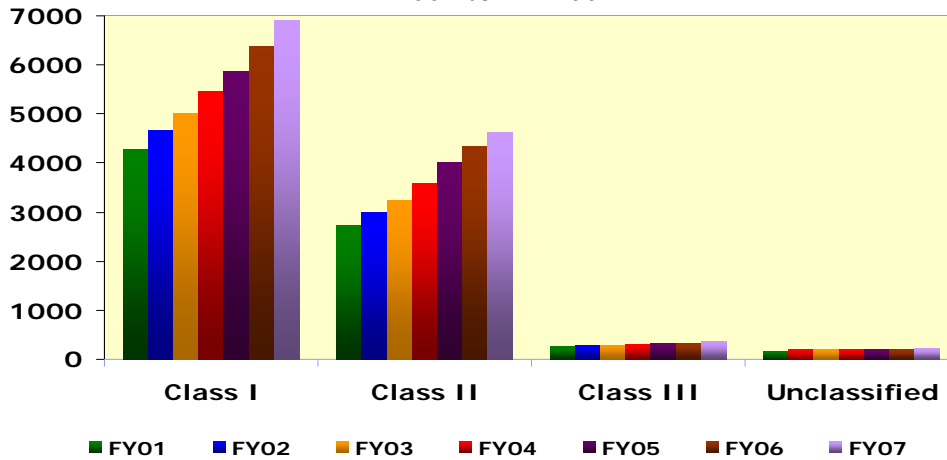


Figure 3:

**Number of Foreign Medical Device Establishments by Device Class
FY 2001 to FY 2007**



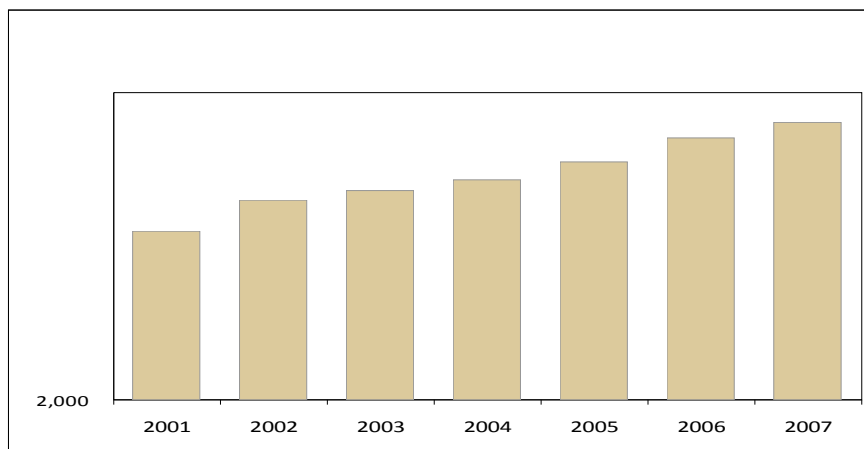
The growth in imports and foreign facilities can have a significant impact on supply chain safety because foreign-made products move through complex foreign distribution chains over which FDA may not have authority and about which FDA has less information than for the domestic supply chain. Such information is necessary to make informed decisions about where to target surveillance, sampling, and inspection resources, based on risk.

manufacturers, which has also grown significantly, and Figure 3 does not necessarily depict device component manufacturers, which may not be required to register.

B. Consumers Are Using More Medical Products

According to a variety of measures, Americans are using more FDA-regulated products. For example per capita prescription use by Americans has grown from 10.9 in 2001 to 12.7 in 2007 (see Figure 4). According to 2008 testimony by then-CBO Director, Dr. Peter Orszag, the general consensus among health economists is that growth in real spending on health care has principally been the result of the emergence of new medical technologies and services, and their adoption and widespread diffusion by the U.S. health care system⁷. Therefore, medical product supply chain safety problems can affect a greater number of people than they did a few years ago.⁸

Figure 4:



C. There are Greater Opportunities for Economically Motivated Adulteration

Several factors suggest that there are more opportunities and greater incentives for economically motivated adulteration (EMA)⁹ of medical products now than there have been in the past. For example, with increasingly complex supply chains come greater opportunities for EMA; more parties and transfers between parties in a supply chain means there are more physical and temporal opportunities to adulterate a product. Likewise, the proliferation of source materials, ingredients, components, and products made in countries that lack mature regulatory systems increases opportunities for EMA. Additionally, as drug prices increase, there is greater economic incentive for

⁷ Source: "Growth in Health Care Costs," Congressional Budget Office testimony, January 31, 2008 (see <http://www.cbo.gov/ftpdocs/89xx/doc8948/01-31-HealthTestimony.pdf>)

⁸ This statement says nothing about the *rate* of adverse events or their degree of seriousness. However, even if the overall rate of adverse events is stable or diminishing, an increase in the use of FDA-regulated products may lead to an increase in the absolute number of adverse events.

⁹ Economically motivated adulteration (EMA) is the fraudulent, intentional substitution or addition of a substance in a product for the purpose of increasing the apparent value of the product or reducing the cost of its production, i.e., for economic gain. EMA includes dilution of products with increased quantities of an already present substance (e.g., increasing inactive ingredients of a drug with a resulting reduction in strength of the finished product) to the extent that such dilution poses a known or possible health risk to consumers, as well as the addition or substitution of substances in order to mask dilution.

unscrupulous parties to adulterate medical products. Finally, in many cases, there may be increased difficulty in detecting EMA, as appropriate test methods may not exist or sophisticated scientific equipment may not be readily available to detect EMA.

Though reliable data on the frequency of EMA is difficult to obtain, a number of specific cases where adulteration has been detected indicates that EMA may be on the rise.¹⁰ The severity of consumer risk posed by these events is substantial and has been well publicized. These cases include contamination of Chinese heparin with oversulfated chondroitin sulfate (OCOS) and diethylene glycol (DEG)-tainted glycerin in Chinese-made toothpaste.

FDA's four-part approach is aimed at addressing these challenges.

II. TAKING A COMPREHENSIVE APPROACH TO SUPPLY CHAIN SAFETY

Four main strategies constitute the foundation of FDA's comprehensive approach to medical product supply chain safety. Together, these four strategies—*focusing on prevention, enhancing regulatory information, improving FDA's scientific and analytic capabilities*, and *expanding risk based inspection and enforcement*—provide a framework for the integrated approach that FDA is using to improve medical product safety. FDA is implementing this approach in collaboration and coordination with key public health partners, such as foreign governments.

These strategies aim to identify the source and magnitude of risks along the supply chain, place responsibility where it belongs, and to promote effective actions to reduce these risks and prevent harm. They leverage science and modern technology systems to address intentional and unintentional contamination as well as counterfeiting and diversion¹¹. Below, we briefly describe each strategy, explain what FDA is already doing to implement the strategy, and, where appropriate, describe steps FDA plans to take to improve outcomes.

A. Focus on Prevention

Focusing on prevention is FDA's primary strategy because preventing harm to consumers is FDA's first priority. Historically, medical product supply chain safety efforts focused on detecting problems through FDA inspection at medical product establishments and at ports of entry when a product was offered for import into the United States. While inspection remains an integral part of FDA's approach to medical product safety (see Expand Risk Based Inspection and Enforcement, below), FDA has taken additional steps

¹⁰ At an October 31, 2008, meeting of FDA's Science Board, FDA presented a conceptual model of EMA. FDA described circumstances and factors that are likely to lead to EMA, and pointed to certain types of information that may be useful in trying to prevent EMA. In response to the feedback obtained during the Science Board Meeting, FDA formed an internal working group focused on predicting and addressing EMA. In May 2009, FDA convened a public meeting focused on ways to predict EMA.

¹¹ Diversion is the distribution of product outside the normal commercial chain; also called "gray markets."

to shift its focus to preventing problems before they occur. FDA is focusing on prevention in several ways, including the implementation of quality management systems across the supply chain, harmonizing FDA standards with the international community, launching the Beyond our Borders initiative; developing Good Importer Practices (GIPs); and setting out a foundation for a track and trace system.

1. Implement quality management systems

Increasing industry accountability to prevent harm to consumers is critical to an effective medical product safety system. The cornerstone of a prevention-focused approach in the sourcing of ingredients or components and the manufacturing and distribution of medical products is the implementation of a quality management system (QMS) approach. A QMS approach addresses the safety, quality, and security responsibilities of all persons who manufacture products, including starting materials, for sale to U.S. consumers. QMS builds on current Good Manufacturing Practice (CGMP) requirements, recognizing that supply chain integrity and product safety and quality must be every manufacturer's responsibility.

To reduce risks, manufacturers should build quality into the manufacturing of their products and implement effective preventive measures at their facility, as well as ensure the implementation of such measures at their suppliers' facilities. Manufacturers should be accountable for assessing the hazards introduced by their operations and those of their suppliers and consignees, implementing QMS, monitoring for problems before they result in harm to consumers, taking swift corrective actions to prevent recurrence of any hazards that are not effectively managed and assuring that medical products that leave their facilities are safe and effective.

FDA has taken steps to foster the adoption of QMS by the medical products industry. In 2008, FDA issued two important quality-related guidance documents. The first guidance document, *Process Validation: General Principles and Practices*,¹² is a draft guidance that incorporates a modernization and quality systems approach to the validation of manufacturing processes. The second guidance, International Conference on Harmonization (ICH) *Q10 Pharmaceutical Quality System*¹³, is a final guidance that provides for an internationally harmonized framework for timely and continual improvements of pharmaceutical products throughout their life cycle by applying QMS principles.

FDA is developing a modern risk-based pharmaceutical quality assessment system that focuses on critical drug quality attributes and how they relate to a drug's safety and effectiveness. FDA implemented a pilot program involving the voluntary submission of quality (chemistry, manufacturing, and controls) information for drug products in an expanded change protocol, consistent with the principles of quality by design (QbD) and risk management in pharmaceutical manufacturing. Out of 11 submissions received, 9 were reviewed and approved and 2 are currently under review. This program provided

¹² See <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf>

¹³ See <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073517.pdf>

both FDA and industry with valuable experience in implementing QbD principles, which enables risk-based regulatory decisions. The knowledge gained is now incorporated into harmonized international regulatory guidances on pharmaceutical development. As a result, FDA is receiving an increasing number of submissions containing QbD elements, with 33 new submissions received through May 2009. The success of this pilot initiative is now being extended to therapeutic biologic products in a similar program announced on July 2, 2008, which will facilitate manufacturing innovation and continuous improvement throughout a biologic product's life cycle.

2. *Increase harmonization*

In the global marketplace the use of the same safety standards by FDA and other countries that manufacture or distribute medical products for the U.S. can improve medical product safety by making it easier to leverage the oversight capabilities of other countries while reducing the burden on industry to receive approval and market their products in more than one country. To achieve this objective, FDA is engaged in several efforts directed at international harmonization.

The Guidance for Industry: *Q10 Pharmaceutical Quality System* described above is an internationally harmonized guidance (part of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)¹⁴). This means that FDA's standards and recommendations for an effective quality management system are harmonized with those of other ICH members. By creating a uniform framework, FDA anticipates that industry will adopt effective quality management systems, because a compliant system will satisfy the requirements of multiple regulatory bodies.

Likewise, for medical devices, FDA is evaluating how its Quality System Regulations (21 CFR Part 820) may harmonize for medical devices with ISO 13485, an international standard that represents the requirements for a comprehensive management system for the design and manufacture of medical products. Many countries rely on ISO standards in regulating medical devices. By harmonizing its regulations, FDA and device regulatory agencies from other countries can more readily rely on one another's inspections and exchange inspection reports in a meaningful way.

FDA continues to support global harmonization of inspections through collaborations with multiple third-party auditing organizations and foreign governments. The Accredited Persons (AP) Third-Party Inspection Program has been active since 2005¹⁵.

¹⁴ ICH brings together the pharmaceutical regulatory authorities of the United States, Europe and Japan, as well as experts from the pharmaceutical industry, with the goal of recommending ways to achieve greater harmonization in the interpretation and application of technical guidelines and requirements.

¹⁵ The AP Third-Party Inspection Program allows third parties recognized by FDA to: assess the quality system of eligible manufacturers of Class II and III medical devices; determine compliance with other device requirements in statute and regulations; and prepare and submit reports to FDA, who makes the final compliance assessment. For more information see <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/ThirdPartyInspection/ucm125410.htm#overview>.

Since then, more than 20 quality systems inspections have been completed by FDA-trained third-party auditors, about half of these outside of the United States. Finally, FDA has also been active on the Global Harmonization Task Force (GHTF)¹⁶, including efforts to develop a common audit form for medical device inspections. A common audit form will allow whoever is performing a device inspection to assess compliance with harmonized standards. Harmonizing quality management systems standards, using a common audit reporting form, and developing international standards for conducting an inspection would allow FDA and its regulatory counterpart to ultimately coordinate and rely on one another's inspections. This will reduce costs by avoiding duplicative efforts as well as increase the level of protection government agencies provide through greater understanding and oversight of the supply chain.

3. *Strengthen beyond our borders initiative*

Foreign governments are essential public health partners in protecting the medical product supply chain. To facilitate our activities in and collaborations with other countries, in December, 2008, FDA launched an initiative called "Beyond Our Borders," which recognizes that:

- many products come from countries with limited ability to provide the regulatory oversight needed to ensure the safety of the products exported
- lax oversight in some such jurisdictions may present opportunities for products to be unintentionally contaminated, or intentionally contaminated by those who mean harm, by counterfeiters, or by those who try to profit by "cutting corners"
- working more closely with counterpart agencies in other countries allows FDA to be more efficient and thorough in performing its oversight responsibilities.

The Beyond Our Borders initiative seeks to address international challenges to public health and national security by increasing collaboration with FDA's foreign counterparts – many of which are highly effective and share high standards – providing technical assistance to foreign regulators and industries, establishing methods to learn more about foreign exporters, and establishing overseas offices within some foreign countries.

a. *Increase collaboration*

During the past five years, the number of agreements FDA has entered into with its regulatory counterparts throughout the world has more than doubled, and it continues to grow. FDA has 113 memoranda of understanding and other arrangements with its counterparts in 25 countries, the European Union, the Council of Europe, and the World Health Organization.

¹⁶ The GHTF fosters international harmonization in the regulation of medical devices, by bringing together regulatory and industry authorities from the United States, the European Union, Canada, Australia and Japan to encourage the harmonization of regulatory practices to ensure the safety, effectiveness, and quality of medical devices.

These arrangements enhance the ability of FDA and its counterparts to share human, scientific, and investigational resources and knowledge, share scientific expertise, and promote responsible international standards and regulations. Many of these arrangements allow the sharing of inspection reports and other non-public information. FDA intends to use these arrangements more extensively to obtain information that can help FDA more effectively identify which foreign-made or sourced products present risks to American consumers and more effectively target its resources to protect public health.

b. Learn more about foreign exporters

Foreign manufacturers that export FDA-regulated products to the United States must register their company and product information with FDA. However, FDA has been unable to verify all of the information provided by the many manufacturers. Under the Beyond the Border Initiative, FDA is working to enlist the help of non-government organizations to visit the foreign facilities to verify that the manufacturers exist and that they manufacture the products listed in FDA's records.

FDA is also working to verify that products made or processed overseas conform to FDA safety standards and requirements before they are imported. These third-party resources may include foreign government agencies and independent organizations that have been accredited by FDA or accreditation organizations recognized by FDA. This verification would complement FDA's own inspections and other regulatory activities.

c. Provide technical assistance

A large portion of the nation's increased trade volume comes from countries with developing economies and developing regulatory authorities. FDA is frequently asked to partner with these countries as their public health and regulatory officials work to enhance their systems. FDA is helping these foreign regulators and foreign industries to understand FDA standards, laws, and regulations. FDA is developing a database to more effectively track our technical assistance programs and assess the outcomes of those activities.

As part of this effort, FDA has continued its outreach efforts on quality management systems, holding several workshops to solicit public input on related issues. Workshops have been held in the United States and in other countries (e.g., Dublin in 2007; Shanghai and Beijing in 2008).

d. Establish overseas offices

FDA is continuing to establish offices overseas in parts of the world where the agency believes a much closer working relationship with its counterpart regulators

will help FDA to more effectively meet its responsibilities. FDA's in-country offices will allow the agency to:

- build or further strengthen a trusted regulator-to-regulator relationship
- learn more about the industries and understand the challenges of how products are regulated in these countries
- more easily inspect manufacturing and processing facilities in these countries or determine how FDA can further leverage inspections already performed by its counterparts in certain regions, such as Europe
- have increased interactions with foreign manufacturers to help ensure that products shipped to the United States meet FDA standards for safety, efficacy, and manufacturing quality
- verify that imported products and the way they are manufactured meet U.S. health and safety requirements.

In November 2008, FDA opened its first overseas office in China. FDA's China Office is set up to accommodate eight FDA experts from the United States and five local Chinese nationals. In addition to senior technical experts in Beijing, the U.S. contingent includes inspectors who will work out of Shanghai and Guangzhou.

FDA has subsequently opened overseas offices in India, Latin America, and Europe and is in the process of deploying staff to those offices. The India office will include technical experts and inspectors. because India is a major exporter of FDA-regulated products. The Latin America office, headquartered in Costa Rica, with additional offices to be established in Mexico and Chile, will deploy technical experts in the three countries to enhance product safety in the region and use U.S.-based inspectors to conduct inspections. The European offices focus on enhancing cooperation and leveraging resources with our counterpart agencies and are located in Belgium, the United Kingdom (working at the European Medicines Agency in London), and Italy (working at the European Food Agency in Parma). Also, FDA plans to open an office in the Middle East, which at this time is being staffed in Rockville, Maryland.

4. *Develop good importer practices (GIPs)*

Importers are uniquely positioned in the supply chain to make sure foreign-made products, ingredients, and components are safe, because they are responsible for bringing those items into the United States. In January 2009, FDA and other federal agencies issued a draft guidance for industry on GIPs¹⁷ to encourage importers to take proactive steps to prevent harm to consumers from the products they import. The guidance sets out recommendations to importers of products, including FDA-regulated products, on practices and procedures to follow to increase the likelihood the products they import are in compliance with applicable U.S. safety and security requirements. The recommendations are intended to promote and facilitate sound decision making by

¹⁷ See <http://www.fda.gov/RegulatoryInformation/Guidances/ucm125805.htm>

importers about how best to address the product's potential to cause harm and to facilitate compliance with U.S. requirements. GIPs are broadly organized under four guiding principles:

- establishing a product safety management program
- knowing the product and applicable U.S. requirements
- verifying product and firm compliance with U.S. requirements throughout the supply chain and product life cycle
- taking corrective and preventive action when the imported product or firm is not compliant with U.S. requirements.

The goal of GIPs is to encourage importers to institute practices to identify and minimize risks associated with imported products. The draft guidance recommends, generally, that importers should know the producer of the foreign products they purchase and any other manufacturers with which they do business; that they understand the products that they import and the vulnerabilities associated with these products; that they understand the hazards that may arise during the product life cycle, including all stages of production; and that they ensure proper control and monitoring of these hazards.

5. *Establish systems to identify medical products*

Effective track and trace systems can make it more difficult for persons to introduce counterfeit or intentionally adulterated medical products into the U.S. market, make it easier to identify persons responsible for making a product unsafe, and facilitate the recall of unsafe products by more quickly identifying where a product is located in the marketplace.

FDA has worked to establish a foundation for track and trace systems for human drugs. Under Section 505D of the Federal Food, Drug and Cosmetic Act (FDCA), as amended by the Federal Food and Drug Amendments Act of 2007 (FDAAA), Congress granted FDA authority to develop standards to identify, validate, authenticate, and track and trace prescription drugs. The identification standard would enable the serialization of prescription drug product packages with a standardized numerical identifier, which will facilitate the tracking and tracing of the prescription drug along the medical product supply chain. It would also assist trading partners in authenticating drug products.

In March 2008, FDA published in the Federal Register a call for information regarding established, ongoing, or future plans for standards development and technologies that can be used for supply chain security.¹⁸ In January 2009, FDA published a draft guidance entitled “Standards for Securing the Drug Supply Chain – Standardized Numerical Identification for Prescription Drugs.”¹⁹ Currently, FDA is reviewing comments on the draft guidance and is preparing a final guidance to meet the March 2010 statutory deadline for this standard. Work is also underway to develop the other standards, as described in Section 505D of the FDCA.

¹⁸ 73 Fed. Reg. 14988 (Mar. 20, 2008).

¹⁹ See <http://www.fda.gov/RegulatoryInformation/Guidances/ucm125505.htm>.

With respect to medical devices, under Section 519(f) of the FDCA, as amended by FDAAA, Congress granted FDA authority to issue regulations establishing a unique device identification (UDI) system for medical devices. The statute states that the unique identifier must adequately identify the device through distribution and use and may include information on the lot or serial number.

In February 2009, FDA held a public workshop to discuss and invite comment on a number of questions to assist the agency in developing a proposed rule related to establishing a UDI system.²⁰ These questions included: the types of devices or particular devices that should be subject to a UDI system; the characteristics necessary to uniquely identify the device (e.g., the device identifier) and the production identifier (e.g., serial or lot number); the placement of the UDI; the technologies to consider (e.g., linear bar code or 2D bar codes); and the availability of a central, publicly available UDI database and what such a database should contain (e.g., manufacturer, make, model, Global Medical Device Nomenclature code, listing number, attributes, such as whether the device contains latex or is MRI compatible).

FDA intends to issue a proposed rule to establish a UDI system in FY 2010 and to continue its efforts in the international community to work towards global harmonization of device identification. The agency also plans to continue to work on data systems and business processes to prepare for use of UDI information.

B. Enhance Regulatory Information

Because accurate, complete, and timely information is critical to good regulatory decision making, the second strategy in FDA's overall approach to supply chain safety is to enhance the quality and quantity of important regulatory information it receives. Without accurate information about where particular products are made and who in the supply chain is providing and handling products, it is difficult for FDA to effectively target its resources to actions that will provide the greatest public health benefit, such as optimizing a risk-based inspectional regime. To achieve this objective, FDA has undertaken several initiatives to enhance the gathering and maintenance of regulatory information. Examples include making improvements to the agency's IT infrastructure, establishing a harmonized inventory system for medical product facilities, improving the agency's registration and listing system, and expanding information sharing with public health partners.

1. Upgrading FDA information technology (IT) infrastructure

Smart IT investments can provide FDA with the necessary tools to gather, organize, and analyze large amounts of information about the medical products and facilities it regulates and their potential associated risks. FDA has made substantial progress in

²⁰ 74 Fed. Reg. 2601 (Jan. 15, 2009).

modernizing its IT infrastructure. For example, FDA has embarked on several projects to upgrade IT infrastructure in the areas of field investigations and laboratory operations to replace and integrate the functionality of its legacy systems. These new systems can be adapted with greater efficiency as FDA's analytic needs change. The upgraded laboratory system will create an electronic data environment within FDA's regulatory laboratories, including the capture of raw data from automated analytical instruments and electronic completion and storage of analytical worksheets. These IT enhancements will enable high sample throughput rates, thus increasing analytical capacity. Electronic data capture also facilitates the distribution and sharing of methods validation and analytical results with other FDA, Federal and State labs.

In recent years, FDA has made real strides in its effort to achieve a fully automated and interoperable infrastructure for managing the exchange of regulatory medical product information. For example, FDA has been working with international standards organizations to develop and implement standards that will facilitate system interoperability. FDA is also modernizing its MedWatch reporting system to facilitate the reporting by industry, providers, and patients of adverse events likely caused by or problems with an FDA-regulated product.

2. *Harmonizing inventory*

A current project aimed at improving regulatory information is the Harmonized Inventory initiative. This initiative is intended to establish a single coordinated inventory of FDA-regulated firms, facilities, products, components and ingredients, and their points of contact. The harmonized inventory will be linked to all regulatory information pertaining to a unique entity, including product submissions, product approvals, inspections, import entries, sample analysis, recalls, complaints, adverse event reports and compliance actions. Integration of these data sources will provide FDA with a more complete and coherent risk profile of the products and facilities it regulates.

3. *Improving the electronic registration and listing system*

An accurate and complete electronic registration and listing system is imperative to allow FDA to accurately target inspections and identify the location of a medical product manufacturer.

a. *FDAAA implementation*

Section 510(p) of the FDCA, as amended by FDAAA, requires that drug and device establishment registration and listing information be submitted electronically, unless a waiver is granted. Historically, required registration information for establishments that manufacture human drugs has been submitted on paper. Following the enactment of FDAAA, in May 2009, FDA issued guidance entitled *Providing Regulatory Submissions in Electronic Format – Drug*

Establishment Registration and Drug Listing, describing how to make these submissions in an electronic format that FDA can process, review, and archive.²¹

As of June 1, 2009, FDA no longer accepts drug establishment registration and drug listing information in paper format, unless FDA grants a waiver. Moving from a paper-based format to an electronic system will create a more comprehensive and accurate database, which is fundamental to FDA's mission to protect and promote the public health and should also improve the timeliness and accuracy of the submissions. This information will help FDA track problems and more accurately target inspections, thereby increasing product safety.

For devices, FDAAA required FDA to begin implementing electronic registration and listing for all medical device establishments beginning with fiscal year 2008. When FDA implemented this requirement, there was a decrease in the number of establishments that electronically registered in 2008. That year FDA issued more than 15,000 letters to device establishments that failed to electronically register in 2008 to determine their status. As a result, FDA categorized 13,700 establishments as inactive, and removed defunct establishments from FDA's inventory, saving agency resources and allowing a sharper focus on inspection priorities.

b. Guidance – submission of a unique facility identifier (UFI)

The guidance mentioned above not only assists manufacturers with electronic registration and listing by explaining the statutory requirement to submit electronically and recommending how to create a submission in the code recognized by FDA's computer system, it states FDA's intent to use the Data Universal Numbering System (DUNS) as the registration number assigned by the agency and advises registrants to submit their DUNS number with their registration.

The use of DUNS will aid FDA in efforts to link information about registrants across different computer systems and with different agencies. It is expected to result in a more accurate database of FDA-registered entities, which will assist FDA in targeting establishments for inspection, among other things.

4. *Expanding information sharing*

Sharing information between FDA and its public health partners at home and abroad is essential to better inform FDA about the potential risks to consumers from specific medical products and to more effectively leverage the oversight capabilities of other regulatory partners. As discussed above, FDA already has 113 memoranda of understanding and other arrangements with its counterparts in 25 countries, the Council of Europe, the European Union, and the World Health Organization. These memoranda

²¹ See <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072339.pdf>

and arrangements enhance the ability of FDA and its foreign counterparts to share human, scientific, and investigational resources and knowledge, share scientific expertise, and promote responsible international standards and regulations. Many of these arrangements allow the sharing of inspection reports and other otherwise non-public information.

During the past year, FDA also entered into a memorandum of understanding with the Veterans Administration and the Department of Defense to enhance information sharing; promote efficient use of tools and expertise for product risk identification, validation, and analysis; and build infrastructure and processes that meet common needs for evaluating safety, efficacy, pharmacological classification, and use of drugs.

However, current U.S. laws²² restrict FDA's ability to share trade secret and confidential commercial information with its domestic and foreign regulatory partners that could facilitate an inspection or investigation of potential safety problems. In addition, some countries will not share certain non-public information with FDA because of the statutory limits on FDA's ability to assure that the information is protected from public disclosure.

C. Improve FDA's Scientific and Analytic Capabilities

A strong FDA science workforce working with robust analytical tools is vital to a modern medical product safety system. Without the most current science and good risk analysis, FDA cannot perform its mission effectively and efficiently. FDA has taken several actions to achieve this objective, including increasing its capacity to advance scientific approaches, identifying and piloting innovative uses of new technologies, and using and refining state-of-the-art risk management.

1. Identifying and testing innovative uses of new technologies

To improve efficiency and cost effectiveness of drug product quality management systems and promote development and industry adoption of new technologies and quality by design, FDA has identified and encouraged a number of pilot projects. Collectively, these projects are aimed at implementing FDA's long-standing recognition that a critical aspect of drug safety is drug quality. (Consumers are at risk if a drug is not manufactured in such a way that ensures that it has the necessary identity, strength, quality, and purity.) Since 2004, FDA has been implementing a modernized regulatory system for product quality. Many projects have been launched and completed under FDA's Pharmaceutical Quality for the 21st Century initiative. This program encompasses cross-cutting activities and systems in the quality program's review, compliance, and inspection units. FDA's quality initiative has a number of important goals.

- provide the regulatory policy framework to enable industry adoption of technological advances that promote drug quality assurance

²² See, e.g., 21 U.S.C 331(j); The Trade Secrets Act, 18 USC 1905; The Freedom of Information Act, 5 U.S.C. 552(b)(4).

- provide the regulatory policy framework to facilitate increased reliance on quality systems that will continually improve the quality of drugs and drug manufacturing
- enhance the consistency and coordination of FDA's drug approval and drug quality regulatory programs, in part, by integrating enhanced quality management systems into review and inspection processes
- encourage implementation of risk-based approaches that focus both industry and agency attention on critical areas
- ensure that regulatory review and inspection policies are performed by well-trained staff who are well-versed in state-of-the-art pharmaceutical science

Examples of more recently initiated, ongoing, or completed activities related to applying quality management systems approaches to FDA business processes and regulatory policies concerning review and inspection activities include

- FDA's launch of an initiative to use risk modeling to select the most appropriate sites for routine CGMP surveillance
- FDA's initiation of a pilot program to inspect active pharmaceutical ingredient manufacturing sites in developing nations in collaboration with fellow regulators.

2. *Using and refining state-of-the-art risk management*

One of FDA's most important initiatives is to continue the agency's evolution of cutting-edge practices for risk management.²³

FDA is working to apply qualitative and quantitative techniques to risk analyses, depending on the circumstance and criteria established by specific analytical disciplines. Both newly emergent and known public health risks are part of the rapidly globalizing and increasingly complex medical product supply chain. One of the challenges in transforming FDA into a state-of-the-art risk management organization is that classical paradigms of government risk analysis call for analytically rich, cross-functional analyses that take months or years to reach quantitatively defensible conclusions. The evolving, state-of-the-art risk analysis calls for front-loading the analysis with risk-based decision support systems that can be used to support quick regulatory decision making during public health emergencies and to prioritize known risks for resource allocations.

FDA is implementing risk analysis in an agile, anticipatory mode. This means fostering data intra-operability across FDA information systems and also creating real-time decision support infrastructure and operative procedures. Access to non-traditional data sources, both commercial and governmental, will improve FDA's ability to engage in real-time risk assessment and triage of emerging public health risks.

²³ For the purposes of this report, risk management is the process of identifying, analyzing, evaluating, and reducing or controlling risks. *Risk* refers to the likelihood and severity of harm. In turn, *harm* relates to a reduction in public health. FDA uses risk-based approaches to provide decision makers with tools and data that can be used to prioritize activities and resources based on public health outcomes. Data gaps, poor data quality, and lack of methodology can all reduce the effectiveness of a risk management strategy. The overarching goal for FDA risk management is to link FDA decisions to a positive public health impact.

FDA is implementing the Predictive Risk-based Evaluation for Dynamic Import Compliance Targeting (PREDICT) system. PREDICT will replace the admissibility screening portion of FDA's legacy systems for the processing of import entries. PREDICT can automate most of the marketing status database lookups, which FDA staff must now perform manually for medical products on multiple center systems. PREDICT uses open-source intelligence (the retrieval of relevant risk information from public sources), automated data mining (primarily queries of FDA databases), and pattern discovery techniques. It considers the likelihood that individual shipments are adulterated, misbranded, or otherwise in violation of the law and will flag or generate a numerical, risk-based score for each entry line. Lines that have higher scores or have been flagged for special consideration will be presented to FDA entry review staff, complete with scores and background data. PREDICT has been pilot-tested for seafood imports. FDA plans to begin to expand the use of PREDICT to medical products in the coming months.

D. Expand Risk-Based Inspection and Enforcement

Inspection is a cornerstone of confidence in medical product safety. Inspection and enforcement are critical tools to deter risky and criminal behavior. FDA is increasing the number of inspections it performs, leveraging third-party inspections and pursuing other methods of verification with safety standards (such as certification). Additionally, FDA has launched the Secure Supply Chain pilot and is seeking credible deterrence through increased enforcement.

1. Increasing FDA inspections

In early 2009, FDA established a dedicated foreign drug cadre to augment its existing foreign inspection program. Cadre members are only assigned to foreign inspection work. So far, the group consists of 13 investigators and 2 laboratory analysts, who are responsible for conducting 270 foreign drug inspections this year. FDA intends to expand the cadre over time.

For FY 2009, FDA expects to conduct 6,520 domestic medical product inspections and 915 foreign medical product inspections. The President's FY 2010 budget will allow FDA 590 more domestic medical product inspections and 200 more foreign medical product inspections by the end of FY 2013. The number of inspections during FY 2013 assumes the enactment of the FY 2010 budget and account for the training of new hires.

In addition to inspections performed by FDA itself, the agency continues to leverage the inspectional resources of other governments and third parties. As discussed in the sections Focus on Prevention and Enhance Regulatory Information, FDA will continue to collaborate with international partners to harmonize regulatory and inspectional standards and to extend its regulatory reach through exchanging information with regulatory partners to the greatest possible extent.

In November 2008, FDA, European Medicines Agency (EMA), and Australia's Therapeutic Goods Administration (TGA) began a pilot project involving active pharmaceutical ingredient inspection. The goal of the pilot is to determine if greater international collaboration and information sharing can better distribute inspection capacity, enabling more sites to be monitored and reducing unnecessary duplication. FDA, EMA, and TGA are sharing prospective and retrospective inspectional information and, in some cases, planning joint inspections of facilities in certain countries that manufacture starting materials for many of the drugs taken by Americans, Australians, and Europeans. FDA plans to collaborate with EMA and TGA on the inspection of more than 25 drug facilities.

2. *Increasing other methods of verification*

In an increasingly globalized environment, FDA is exploring different models of verification of compliance with FDA safety standards, such as inspections and certifications by third parties.

For example, FDA and Health Canada have started a joint inspection pilot program (the Pilot Multi-Purpose Audit Program), in which trained third-party auditors can conduct inspections and audits of device manufacturers, to assess compliance with U.S. quality system regulations and the ISO 13485 Standard, which Health Canada has adopted. These inspections have resulted in substantial time savings at the manufacturing facilities while verifying the firm's compliance with two separate sets of regulatory requirements. As of February 2009, a total of six inspections have been completed. Collaborative inspections like these have the potential to reduce FDA regulatory burden for both foreign and domestic manufacturers for Class II (moderate risk) and Class III (high-risk) devices, in addition to enabling FDA to use its inspectional resources more efficiently. FDA is also exploring the use of third-party certification by excipient manufacturers to verify compliance with FDA requirements.

3. *Launched a secure supply chain (SSC) pilot*

A recent pilot program jointly administered by FDA's CDER and ORA promotes additional accountability of medical product manufacturers. The SSC program, a voluntary initiative, is aimed at promoting the safety of drugs and active pharmaceutical ingredients produced outside the United States by requiring participants to be in control of their product from manufacture through importation. Under the pilot, FDA intends to select up to 100 applicants who hold an FDA-approved drug application or who are the foreign manufacturers identified in an FDA-approved application. To participate, these entities must have a plan in place to maintain control of their product along the supply chain. The applicants agree to correct concerns identified by FDA and comply with record-keeping requirements. The SSC program is limited to imported active pharmaceutical ingredients that are used to make FDA-approved drugs. Foreign drug manufacturers and U.S. establishments receiving drugs must be FDA-registered and comply with CGMP, and applicants must show that their drug products use a secure supply chain.

The goal of the SSC pilot is to enable the agency to determine the practicality of using a secure supply chain program to assist the agency in efforts to prevent the importation of drugs that do not comply with applicable FDA requirements. Such a program, broadly applied, would enable FDA to focus its resources on manufacturers and importers who are not part of the program and who may not be compliant with applicable standards. Participation in the program will result in increased likelihood of expedited entry for specific finished drug products and APIs imported into the United States and provide added assurance of safety for the products in the program.

4. *Achieving credible deterrence through increased enforcement*

Appropriate and active enforcement can be an effective deterrent to future risky and criminal behaviors that place consumers at risk.

- Significant actions with regard to contaminated or unapproved drugs

During 2008, FDA undertook a series of advisory and enforcement actions with the goal of protecting the U.S. consumer. A vastly abbreviated list of some of the most significant of these actions includes resolution of the previously mentioned heparin incident; issuance, in September 2008, of two Warning Letters and an Import Alert covering 30 different generic drugs following inspections of two Indian facilities owned by Ranbaxy Laboratories, Ltd. that documented significant deviations from CGMP; and action, culminating in a consent decree, against Actavis Totowa, LLC, for significant and repetitive CGMP violations and for distributing unapproved drugs.

In addition, in FY 2008, FDA issued 250 Warning Letters and more than 50 Untitled Letters related to medical products.

- Significant actions with regard to counterfeits

FDA recently brought to conclusion a significant action involving Chinese counterfeit pharmaceuticals. In 2006, FDA initiated a criminal investigation that subsequently identified Kevin Xu, 36, a citizen of the Peoples' Republic of China, as the source of numerous counterfeit pharmaceuticals. Xu was arrested and subsequently prosecuted in the United States and sentenced in January 2009 to serve 78 months in federal prison without parole, the maximum sentence under the applicable U.S. Sentencing Commission guideline for conspiring with others in the Peoples' Republic of China to traffic in counterfeit drugs and causing the introduction of counterfeit and misbranded drugs into interstate commerce. In addition to the prison term, the court ordered Xu to pay \$1,286,060 in restitution with \$128,363 to Pfizer Pharmaceuticals and \$1,157,697 to Eli Lilly Pharmaceutical Company.

III. OPPORTUNITIES FOR FY 2010

The President's FY 2010 budget request for FDA totals \$3.2 billion and includes increased funding for medical product safety. With the requested funds, FDA will be able to hire more than 300 additional staff and implement a broad range of activities to improve the safety and security of foreign and domestic sources of medical product ingredients, components, and finished products all along the medical product supply chain. Planned activities include the following:

- Increase foreign and domestic medical product inspections and other field activities conducted by ORA
- Improve laboratory infrastructure to increase the volume of sample analysis
- Provide technical support to FDA foreign offices and field operations conducting foreign and domestic device manufacturing inspections
- Provide on-site training to foreign regulators on medical device safety and quality standards
- Create and translate computerized training classes on medical device safety and quality standards into several languages.
- Verify registration of medical device establishments
- Develop and issue regulations on a unique device identification system
- Increase technical support for foreign and domestic inspections and enhance risk analysis tools for biologic products
- Develop quality systems for product testing and lot release of biological products
- Strengthen science and computing to ensure that FDA can adequately regulate new drug manufacturing technologies
- Identify and improve enforcement against Internet sites that expose consumers to unapproved drug products and fraudulently marketed drug products
- Modernize and enhance information technology systems to collect, store, and analyze regulatory, scientific, and risk-based information necessary to ensure the safety and effectiveness of medical products.

IV. CONCLUSION

Providing patients with safe and effective medical products is a vital part of FDA's mission to protect and promote the public health.

FDA is committed to implementing a modern medical product safety system that focuses on prevention, provides enhanced regulatory information to FDA, is supported by improved FDA scientific and analytic capabilities, and expands risk-based inspections

and enforcement. FDA has already taken many steps in furtherance of its comprehensive approach to improving medical product safety; we have implemented a wide range of new initiatives and instituted policies that are aimed at making sure that American consumers receive only safe medical products.

At the same time, FDA recognizes that its approach must continue to evolve and remain flexible, as challenges to the medical product supply chain will also continue to evolve.

Although we have made significant progress, much remains. We look forward to working with Congress and our other partners on additional ways to maintain a modern safety system so that Americans have the safe and effective medical products they rightly deserve.