



**STATEMENT OF**

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**“FDA Actions to Improve Safety of Medical Products with Foreign  
Components”**

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## **INTRODUCTION**

Mr. Chairman and Members of the Subcommittee, I am Andrew C. von Eschenbach, M.D., Commissioner of Food and Drugs. Thank you for the opportunity to discuss the U.S. Food and Drug Administration's (FDA or the Agency) progress in responding to the challenges created by drugs for the U.S. market that are either fully manufactured overseas or that are manufactured in the U.S., but contain foreign components. FDA's mission is to ensure that safe and effective drugs are available to patients, regardless of where they are produced. Globalization, increased product complexity, and other market developments are placing tremendous strains on our import safety system. The multiple and complex changes facing us in the 21<sup>st</sup> century pose challenges for our import safety system that we are working to address. In my testimony today, I would like to outline the Agency's systems-based approach to address these challenges.

## **21<sup>ST</sup> CENTURY CHALLENGES TO OUR DRUG DELIVERY SYSTEM**

Any entity that intends to import drugs or drug components into the U.S., in compliance with the Federal Food, Drug, and Cosmetic (FD&C) Act, must ensure, among other things, that the drug meets a number of manufacturing quality and product labeling requirements. In the FD&C Act, Congress created a "closed" distribution system for domestically and internationally manufactured drug products to help ensure the domestic supply is safe and effective. In this "closed" distribution system, all prescription drugs, whether manufactured in the U.S. or abroad, must be approved by FDA as "safe and effective" for their intended use prior to marketing in the U.S. In order for a product to be determined "safe," it must be manufactured in ways that assure the continued quality of the product with each new batch or production quantity and that assure that changes in the manufacturing processes do not result in changes to the product's clinical safety and

efficacy profile. Because of this, FDA prescription drug approvals are manufacturer-specific and product-specific, and include many requirements related to the product's manufacture, such as manufacturing location, formulation, source and specifications of active ingredients, manufacturing controls, the container/closure system specifications, and product labeling. Facilities, be they domestic or foreign, that manufacture drugs for the U.S. market must meet FDA's current good manufacturing practice (cGMP) requirements.

FDA's regulation of drug products is considered one of the international "gold-standards," and our goal is not only to maintain that standard but continually strive for improvement. We do not, however, operate in isolation, but instead in the context of a rapidly-evolving world in which local markets deliver products produced, in whole or in part, anywhere in the world. The domestic production-to-consumption system of the past is changing to reflect the globalization trends of today. Source materials and production sites can be oceans apart. The complexity of products and their components grows alongside an industry that is dispersed and decentralized. The rate of imported FDA-regulated goods has grown dramatically over the last decade. This trend will continue, presenting FDA with the significant challenge of regulating a lengthening supply chain with a shortened distribution time. These changes are challenging the Agency's import safety system in the 21<sup>st</sup> century.

## **FDA'S SYSTEM-BASED APPROACH TO A SYSTEMIC PROBLEM**

FDA is responding to these changes by building systems that better identify and prioritize potential risks all along the product's life-cycle. This involves significant challenges with regard to imported products. FDA needs a more continuous stream of information about the risks posed along the entire life-cycle of imported products, and the ways in

which manufacturers, transporters, importers, and distributors are addressing those risks. Such information will allow FDA to target its resources in the most efficient manner to best protect public health.

To facilitate these and other import safety needs, the President issued an Executive Order on July 18, 2007, which established the Interagency Working Group on Import Safety (Working Group). The Working Group recently presented the President with an Action Plan for Import Safety. FDA's implementation of the Action Plan addresses the needs of a globalized economy, which demands heightened regulatory interoperability, information exchange, and cooperation with foreign regulatory partners, especially on product quality and enforcement matters. The following describes FDA's life-cycle approach – based on this Action Plan - to improving the compliance of foreign drug manufacturers with U.S. regulations. This life-cycle approach provides a science-led, risk-based system to help keep Americans safe by *preventing* harm before it can occur, enhancing our *intervention* methods at key points in the distribution system when risks are identified, and by strengthening our ability to *respond* immediately when harm has occurred or is imminent.

### **Preventing Harm Before It Can Occur**

The U.S. border must become one of several integrated checkpoints to verify that imported products comply, including in their manufacture, with U.S. health and safety requirements. In other words, FDA must further shift from “gate-keeper” to a stronger and more comprehensive import safety authority. Imported drugs and devices must be safe and effective and must meet all applicable FDA standards *prior* to reaching U.S.

ports-of-entry. FDA is taking many actions to prevent harm to the American consumer before medical products reach our border.

*Maximizing Foreign Prescription Drug Pre-Approval Inspections.* Prior to the approval of a new drug application (NDA) or abbreviated new drug application (ANDA), FDA determines that the manufacturing processes for the active pharmaceutical ingredients (API) and finished dosage form of the drug are adequate to preserve the drug's identity, strength, quality and purity. FDA performs hundreds of foreign prescription drug manufacturing inspections per year. Most of these foreign inspections are pre-approval, cGMP inspections designed to evaluate the capability of manufacturing facilities to generate a safe and high-quality product. FDA conducted more foreign drug inspections in fiscal year (FY) 2007 (498) than any other prior fiscal year in the Agency's history. This is a marked increase over the past few years as well, compared to 374 in FY 2004, 370 in FY 2005, and 342 in FY 2006. Exercising FDA's regulatory authority is challenging. In some countries, we need authorization from that government to enter and inspect facilities. In some cases, the U.S. Department of State issues travel alerts and travel warnings that require FDA to appropriately take special precautions to ensure the safety of our investigators in these locations.

Foreign inspections are more costly than similar inspections of domestic facilities because of travel costs and special needs associated with travel abroad. There are approximately 800 FDA investigators trained to conduct foreign inspections in all program areas and 335 specifically for the drug program area. FDA relies on assistance from the firms' U.S. agents and representatives to translate if needed and help with logistical challenges that arise in traveling to foreign facilities. In certain circumstances, FDA can obtain help in these areas from U.S. Embassy and HHS personnel stationed in

the country in which an inspection is scheduled. While FDA is committed to increasing the number of foreign inspections.

*Beyond Our Borders Initiative.* FDA's Beyond Our Borders Initiative is a systems-based approach to the systemic problem of the Agency's regulation of food, cosmetics, and medical products. The Beyond Our Borders Initiative includes increased collaboration with foreign regulators, use of third parties to provide information about regulated industry compliance with FDA standards, and providing additional direction to regulated industry for their global activities. This initiative will be financed with existing FY 2008 resources and the President's FY 2009 Request.

FDA has in place more than 70 cooperative arrangements with foreign counterparts. Under the leadership of Secretary Leavitt, for example, HHS signed a Memorandum of Agreement (MOA) with the State Food and Drug Administration of the People's Republic of China in December 2007 to enhance the safety of drugs and medical devices imported into the U.S. from China.

*Sharing Foreign Inspection Reports.* In addition to our cooperative agreements and arrangements, FDA now has over 30 confidentiality arrangements with trusted foreign counterparts, many of which provide for the possibility of sharing inspection reports, redacted of proprietary information. FDA intends to increase the use of these arrangements to obtain useful inspectional information that can help FDA make more informed judgments in the prioritization of foreign inspection activities. Through our negotiation of specific bilateral work plans with other trusted foreign counterpart agencies, we intend to explore opportunities to acquire useful inspection information from established, trusted foreign agencies with which we can establish appropriate

confidentiality arrangements. For example, the European Union (E.U.)-U.S. Bilateral Technical Working Group on Medicines Quality and Manufacturing is focusing on utilizing and leveraging resources through the exchange of inspectional planning data and inspectional observational data for plants in the U.S. and E.U. and in other countries inspected by either the E.U. or the U.S.

*Foreign Presence.* FDA and HHS leadership, the Department of State, and the U.S. Ambassador to China have committed to establishing an FDA office in China. Along with the important MOA signed with two FDA counterpart Chinese agencies, permanent FDA positions in China are a significant step toward ensuring access to safe food, drugs, and medical devices in the global market. FDA's efforts will build stronger cooperative relationships with the FDA's counterpart agencies in China, enhance technical cooperation with these agencies, and foster development of information flow from a regulatory system in China. FDA can rely in part on these efforts in making its risk-based import decisions. The permanent overseas office in China will also allow greater access for FDA inspections and, very importantly, greater interactions between FDA staff and Chinese manufacturers to help assure that products that are shipped to the U.S. meet FDA standards for safety and manufacturing quality.

In addition, an FDA delegation visited counterparts in India to begin conversations to establish appropriate counterpart collaborations in that country. By the end of this year, we are hoping to have established in-country FDA presence in China and limited engagement in India.

*Providing for Certification by Third Parties.* Another component of the Beyond Our Borders Initiative leverages private sector resources. As recommended in the President's

Action Plan for Import Safety, FDA is pursuing expanded use of third party certification to verify compliance with U.S. safety and security standards. These third parties can include foreign government agencies and independent entities who have been accredited by FDA or by an accreditation organization recognized by FDA. Such third-party certifications can provide FDA with helpful information about a firm's compliance with FDA requirements. This certification would not supplant FDA inspectional or other regulatory activities, but would complement them. This information will aid FDA in prioritizing and targeting its compliance and inspection resources toward high-risk situations. The China MOA, for example, includes a provision for a registration program and working toward a system that will enable the Chinese government to certify the status of Chinese firms that manufacture active pharmaceutical ingredients (API) and other components of finished drug products. To support the Chinese registration program, and efforts to work toward a certification program, agencies from the two countries will conduct training programs and activities to cover topics such as inspection methods and clinical trials to ensure safety; will discuss each country's development of relevant technical guidance documents, regulations, and laws. In addition, the Agency is developing a pilot program that would reduce the delay for firms that take pro-active measures when they import finished drug products and APIs.

*Implementing Foreign Vendor Registration Verification.* To help increase information about foreign facilities, FDA also plans to engage external, non-government organizations with foreign offices to conduct on-site verification of the registration data and product listing information of foreign firms shipping regulated products to the U.S. This process would include visiting foreign firms, and verifying and documenting that they exist and manufacture the products that FDA records indicate they export to the U.S.

*Providing Technical Assistance.* Another essential element of the Beyond Our Borders initiative focuses on helping foreign regulators understand FDA standards. To help ensure compliance with FDA laws and regulations, FDA provides technical assistance to counterpart foreign regulators and to foreign industries that engage in trade with the U.S. to help ensure understanding of, and compliance with, U.S. safety and other regulatory requirements. A significant proportion of the U.S.' increased trade volume comes from developing economies. Such countries need information and expertise to help them oversee production of FDA-regulated products to ensure that they meet the applicable legal requirements and can be imported into the U.S. FDA is seeking to provide additional technical assistance to raise the confidence we can all have in the safety of these products.

*Issuing Good Importer Practices (GIPs).* FDA also plans on issuing guidance on GIPs to help the importing community take appropriate steps to ensure the safety of their products.

### **Enhancing Intervention At Key Points**

*Building A Modern IT Infrastructure.* Upgrading FDA's IT systems is one of my top priorities. We expect these improvements will help to target our intervention efforts related to foreign firms. Today, foreign producers must register with FDA before shipping to the U.S. However, because for most firms there is no cost to register, some firms register, but do not actually produce a product or ship products to the U.S. Others may register and then discontinue shipping without any notice to FDA. These practices create uncertainty about the precise number of FDA registered firms among which to

target inspections, often necessitating secondary data-source checking. Importers must also provide information about the product being imported and its manufacturer.

However, our systems do not yet have the capability to automatically verify the accuracy of all of the information submitted. We are working on more effective and efficient solutions to ensure the accuracy and validity of the data in our registration and import information technology (IT) systems. These IT initiatives are within existing FY 2008 resources and the President's FY 2009 Request.

FDA's Bio-informatics Board (BIB) is addressing this issue for FDA. The BIB, in-part, focuses on the issue of establishing accurate information on firms and their products.

We are actively seeking other means to identify duplicate entries, such as those caused by variations in how name and address information is provided. FDA plans to enhance its IT systems in ways that will enable the Agency to better utilize risk-based information from the entire life-cycle of imported products. Many of these improvements will be implemented in the next two years; implementation of a few will extend beyond 2010. These projects will improve data bases, enhance interoperability of systems within the Agency and among other regulatory agencies, and provide better analytical function to assess and control risk.

For example, the Mission Accomplishment and Regulatory Compliance Services (MARCS) program manages the integration, re-engineering, and enhancement of the legacy systems that support FDA field activities. These systems include the Operational and Administrative System for Import Support (OASIS) and other components which support import processing. Improvements include replacing the current process that screens import entries; giving investigators faster access to product information in FDA

databases; improving sample collection/tracking on both desktop and mobile platforms; and developing a broker information center to allow Customs Brokers to quickly exchange information with import reviewers.

In addition to MARCS, FDA is working on a number of related projects that will improve import safety. These include working closely with Customs and Border Protection (CBP) to ensure that its planned Automated Commercial Environment (ACE), a component of the International Trade Data System (ITDS), will provide the functionality long sought by FDA with respect to entry data submitted by import brokers and filers. FDA will also complete its Unified Registration and Listing System (FURLS), an electronic integration of the registration and listing systems currently maintained in the individual Centers. This unified system will allow the Agency to have a more complete and accurate database of FDA-regulated establishments.

Another IT initiative that has the potential to make a dramatic change in FDA's business practices is PREDICT, an automated entry screening system that incorporates relevant risk data from all points in the import life-cycle, including data currently outside FDA databases, to predict and prioritize the highest risk import entries. A pilot test of the PREDICT prototype system was conducted by FDA during the summer of 2007. The pilot was limited to seafood imported through a small number of ports in southern California. Our plan is to expand the prototype to include all food products and then to include all other FDA-regulated commodities.

*Increasing Surveillance Inspections.* In addition to pre-approval inspections, FDA conducts surveillance inspections of domestic and foreign manufactures and uses a risk-

based priority model to determine which facilities may pose a risk to the American consumer. Given the need to use resources for foreign surveillance inspections as efficiently as possible, FDA staff must consider a number of elements in making a risk-based priority determination. In part, these elements include: the complexity of the dosage form coming to the U.S. from the foreign country, the date the facility was last inspected, the compliance history of the firm, the shipping volume and history, and information from the local regulatory authorities regarding the manufacturing quality and regulatory status of the enterprise. As mentioned above, FDA is conducting more inspections than ever and we are committed to conduct more surveillance inspections in an effort to help ensure compliance with cGMP standards and prevent product problems.

*Holding U.S. Manufacturers Accountable.*  The President's Action Plan for Import Safety outlines several action steps intended to help ensure that importers are aware of their responsibility for safe and effective medical products. U.S. manufacturers also have a responsibility to ensure the safety of foreign-manufactured ingredients used for their finished dosages. U.S. manufacturers of finished dosage forms of drugs that import APIs or other components from abroad must examine and test those ingredients before using them in their drug products under cGMP. FDA may inspect a firm's foreign facilities and/or their domestic facilities to determine if the manufacturing facility meets the Agency's quality standards. In addition, FDA inspections routinely evaluate manufacturers' testing and controls of ingredients and supplies. If, during a domestic or foreign inspection, FDA determines that an imported API fails to meet specifications or is not manufactured using cGMP, FDA has several options. FDA may issue an import bulletin instructing staff to test future shipments. The determination may also support an import alert by means of which FDA could detain future imported shipments. Finally,

such a determination may result in delay or denial of approval of the product's U.S. marketing authorization.

### **Rapid Response to Emerging Safety Risk & Product Problems**

When a health threat does emerge with an imported product, FDA must be ready to take immediate action. Above, I have described many ways the Agency is operationalizing its approach to verifying compliance to reward good behavior. At the same time, FDA must respond authoritatively when we find bad actors in the marketplace.

*Making the Border an Integrated Checkpoint.* FDA works with CBP at the border to refuse admission to those products offered for import that appear to violate the FD&C Act. FDA screens 100 percent of the imported APIs and finished form drugs entering the U.S. to determine whether the product is going to the corresponding facility in the approved NDA and whether that facility is registered and listed. In addition, FDA issues Import Alerts for Detention Without Physical Exam (DWPE) when we have sufficient information to refuse future shipments of a product. The border is one of many integrated checkpoints at which FDA can respond to product problems.

*Rapid Deployment of "For Cause" Inspections.* When FDA has information that raises questions, concerns, or problems, it will rapidly conduct domestic or foreign "for cause" inspections. In such cases, the Agency targets a particular firm or product as an inspection priority based on this information and rapidly deploys an inspection team.

*Expanded Use of Track-and-Trace Technologies.* FDA is working towards the capacity to identify and track a product or group of products along the product life-cycle to facilitate the timely recovery of the violative product and reduce the opportunity for harm. The use of track-and-trace technologies will give FDA the ability to connect the

dots and link important life-cycle information back to the point-of-origin. This will also allow the Agency to communicate targeted and accurate information to the consumer.

*Expanding Laboratory Capacity & Development of Rapid Test Methods.* FDA of the 21<sup>st</sup> Century must be an agile, scientifically-sophisticated Agency with the ability to develop rapid test methods for pathogens and other contaminants, and ensure that these test methods are available at ports-of-entry to assist in determining whether a product should be admitted into the U.S. To accomplish this objective, FDA relies on its lab capacity to develop and validate methods to increase the number of threats that can be rapidly detected.

*Ramping Up The Cadre of Field & International Staff.* To meet the challenges posed by the increase in the globalization of U.S. drug development, FDA must strengthen its field and international inspection operations significantly. The sheer volume of products, manufacturing plants, distributors, and import sites demands a more robust inspection force. We hope to increase foreign prescription drug inspections (by 50) and sampling in FY 2009; increase domestic inspections and sampling in FY 2009; improve laboratory infrastructures and tools for rapid analysis; and establish and increase FDA's permanent, in-country international presence in China.

*New Authorities Required.* In addition, FDA is seeking new authorities to help ensure that foreign manufacturers of drug products are in compliance with U.S. law. We recommend statutory authority for FDA to: require certification by third parties, in certain circumstances that imported products meet U.S. importing standards; refuse admission of products for which FDA encounters undue delay, limits, or denials of access to foreign manufacturing sites; expedite destruction of certain unsafe medical products;

and seek asset forfeiture remedies for certain criminal offenses involving fraudulent or counterfeit products.

## **CONCLUSION**

I have described for you the tremendous efforts underway at FDA to operationalize a systematic, life-cycle approach to dealing with the globalized system of drug development – a systems-based approach to a systemic problem. FDA is implementing, and will continue to implement, the Action Plan for Import Safety, but this is only a start. The Agency will learn and adapt as we move forward as part of the larger, on-going Agency transformation into an FDA of the 21<sup>st</sup> century. We need the partnership of Congress to provide the resources and authorities needed for the Agency to enhance our import safety system to handle the multiple and complex changes facing us today. Even with the challenges presented by globalization, the American product supply for drugs and devices continues to be among the safest in the world. We are committed to ensuring that this remains the case. Thank you for the opportunity to testify. I look forward to responding to any questions you may have.