



# Global Engagement

U.S. Food and Drug Administration



“ Today we recognize that to successfully protect U.S. public health, we must think, act, and engage globally. Our interests must be broader than simply those within our own borders. ”

Margaret Hamburg, FDA Commissioner



# Global Engagement

U.S. Food and Drug Administration



## FDA'S MISSION

FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation, and by regulating the manufacture, marketing, and distribution of tobacco products.

FDA is also responsible for advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable; and helping the public get the accurate, science-based information they need to use medicines, and to reduce tobacco use to improve health.

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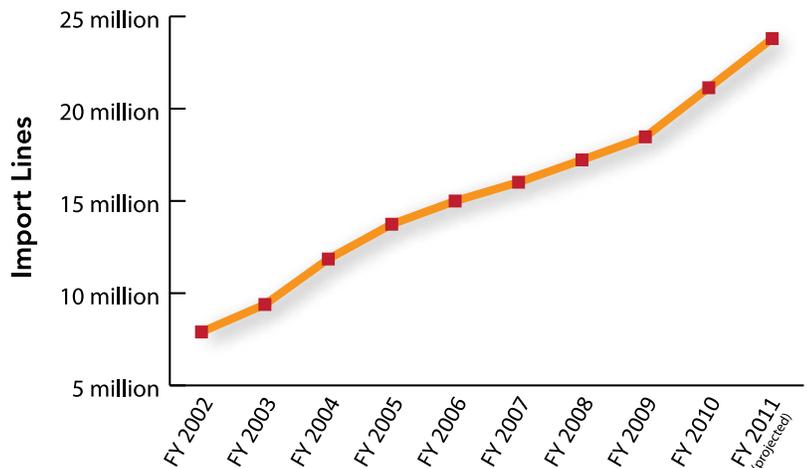


## INTRODUCTION

**S**weeping economic and technological changes have revolutionized international trade over the last several decades, creating a truly global marketplace for goods and services. Accounting for 20 to 25 percent of all U.S. consumer spending, products regulated by the U.S. Food and Drug Administration (FDA) are a substantial component of this global economy.<sup>1</sup> Food and medical products, and their ingredients and components—products that directly and profoundly affect the health and welfare of the U.S. public—are increasingly sourced from abroad. As U.S. consumers continue to demand global products, FDA’s ability to ensure the safety and quality of these imported products will depend on its execution of a myriad of global engagement strategies.

Americans benefit greatly from global sourcing of products. For example, U.S. consumers can choose from a wide variety of fruits and vegetables year round, regardless of the domestic growing season. Health professionals can also draw on drugs and medical devices developed anywhere in the world

**Imports of FDA-Regulated Products Have Grown Dramatically in Recent Years**



FY = U.S. Government fiscal year

NOTE: An import line represents the portion of a shipment listed as a separate item on an import entry document. Items must be listed separately if their tariff description differs from other items in the shipment.

Source: Veneziano, D. 2011. *Import Stats FY 2002-2010*. U.S. FDA, Division of Import Operations and Policy, Office of Regulatory Affairs, Washington, DC.



if they have been approved for use in the United States. But reaping the benefits of the global marketplace requires increased vigilance to protect the U.S. public health.

FDA is responsible for ensuring that imported food, medical products, and other goods it regulates meet the same rigorous standards for safety and quality as those products manufactured domestically. This is a formidable task, requiring FDA to assess millions of products grown, harvested, processed, manufactured, packaged, labeled, and shipped from outside U.S. borders. In 2009 alone, \$2 trillion worth of FDA-regulated products manufactured in more than 300,000 foreign facilities entered the United States from more than 150 countries.<sup>2</sup>



Over the next decade, FDA will continue to transform from a predominantly domestically focused Agency, operating in a globalized economy, to an Agency fully prepared for a regulatory environment in which FDA-regulated products know no borders.

Deborah Autor, FDA Deputy Commissioner for Global Regulatory Operations and Policy

The rapid globalization of commerce presents FDA with many challenges. For example, many products entering the United States are made or grown in countries that lack the necessary regulatory oversight to ensure their quality and safety. Greater numbers of suppliers, more complex products, and intricate multinational supply chains introduce risks to product safety and quality, including more opportunities for economic adulteration and the spread of contaminated products. In the face of these realities, inspection at the U.S. borders or ports-of-entry is no longer sufficient to ensure the safety of the ever-increasing tide of imports to the United States.

### The United States imports:



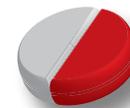
80 percent of active pharmaceutical ingredients



80 percent of seafood



40 percent of finished dosage drugs



Approximately 50 percent of fresh fruit



Approximately 20 percent of fresh vegetables

Sources: Hamburg, M. 2011. *Food and Drugs: Can Safety Be Ensured In a Time of Increased Globalization?* Presented at the Council of Foreign Relations New York Symposium, January 31.

Huang, S. and Huang, K. 2007. *Increased U.S. Imports of Fresh Fruit and Vegetables*. U.S. Department of Agriculture, Economic Research Service, FTS-328-01. Retrieved March 27, 2012, from <http://www.unitedfresh.org/assets/files/Increased%20U.S.%20FFV%20Imports.pdf>.

FDA's success in protecting the U.S. public depends increasingly on its ability to reach beyond U.S. borders and engage with its government regulatory counterparts in other nations, as well as industry and regional and international organizations, to help ensure the quality and safety of products before they reach the United States. Through effective global engagement, FDA is working with its many international partners to weave a global safety net that benefits public health in the United States and around the world.



# GLOBAL CHALLENGES: GLOBAL STRATEGIES

**F**ormed as a consumer protection agency over a century ago, FDA regulates a wide variety of products essential to the U.S. public—food, medical, and radiation-emitting products, as well as pet food, animal feed, tobacco products, and cosmetics. Of these, food and medical products are the most numerous and ubiquitous, influencing the health and welfare of everyone in the United States.

The surge in the volume and complexity of FDA-regulated imports results in increased potential risks to the U.S. public. In recent years, FDA-regulated imports as diverse as cantaloupes, peppers, toothpaste, cough syrup, flu medicine, glucose monitor test strips, glycerin, and a blood-thinning agent known as heparin have all adversely impacted the health of consumers in the United States and around the globe.

To better protect the U.S. public, FDA is utilizing a variety of engagement strategies, in partnership with other agencies and organizations around the world, to strengthen global regulatory capacity; develop and harmonize science-based regulatory standards; increase awareness about the importance of regulatory systems within the broader economic development



**Globalization creates real opportunities to collaborate and leverage our collective expertise and resources. Investments globally are critical to FDA's success domestically.**

Mary Lou Valdez, FDA's Associate  
Commissioner for International Programs

context; and share and analyze information and data globally to enhance regulatory decision-making and facilitate rapid identification of and response to public health emergencies associated from FDA-regulated products. These and other efforts enable FDA to more strategically leverage and optimize its resources for public health protection.



## Food

### The U.S. Public Is Consuming Ever Greater Quantities of Imported Foods

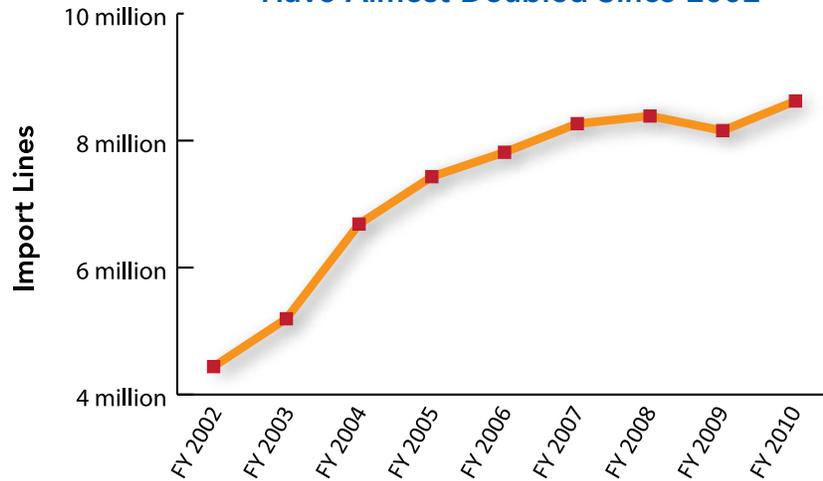
FDA regulates most food products consumed in the United States, from fresh produce to infant formula, as well as food ingredients, supplements, and additives (e.g., food colorings). As of 2011, roughly one in six FDA-regulated food products consumed in the United States is sourced from abroad, and this percentage is much higher for some foods, such as seafood (80 percent) and fresh fruit (approximately 50 percent).<sup>3,4</sup> Many imported foods are dietary essentials (such as fresh fruits and vegetables) or pantry staples (including coffee, tea, and cocoa)—products likely to be consumed daily in almost every U.S. household.

From fiscal years<sup>5</sup> 2002 to 2010, overall U.S. food imports, as measured by the number of “lines” of imported food, almost doubled from 4.4 million to 8.6 million import lines.<sup>6</sup> Imports of fresh fruits, vegetables, coffee, tea, and cocoa have more than doubled since 2000.<sup>7</sup> Based on recent trends, the U.S. public is likely to consume even greater quantities of imported foods in coming years.<sup>8</sup>

## Imported Foods Can Pose Risks to U.S. Consumers

As the volume of imported food increases, so too does the risk that some products will fail to meet FDA standards. The realities of the global marketplace add substantial challenges to FDA's ability to protect U.S. consumers. Less stringent regulations in many source countries, complex supply chains, and longer transit times for imported food all introduce a greater opportunity for contamination, spoilage, adulteration, and counterfeiting.

## Imports of FDA-Regulated Food Have Almost Doubled Since 2002



Source: Veneziano, D. 2011. *Import Stats FY 2002-2010*. U.S. FDA, Division of Import Operations and Policy, Office of Regulatory Affairs, Washington, DC.

## Many FDA Offices and Centers Play Key Roles in Global Engagement\*

**Office of Global Regulatory Operations and Policy (GO)** provides leadership and policy direction to FDA's domestic and international product quality and safety efforts, including global collaboration; global data-sharing; field operations; and compliance and enforcement activities. GO includes:

- ◆ The Office of International Programs (OIP), which leads, manages, and coordinates FDA's global engagement work, and serves as the Agency's primary liaison with foreign governments.
- ◆ The Office of Regulatory Affairs (ORA), which provides FDA leadership on imports, inspections, and enforcement policies to maximize compliance and minimize risk associated with FDA-regulated products.

**Office of Medical Products and Tobacco (OMPT)** provides high-level coordination and leadership across FDA's Centers for drugs, biologics, medical devices, and tobacco products, and oversees the Agency's special medical programs. OMPT includes:

- ◆ The Center for Biologics Evaluation and Research (CBER), which ensures that vaccines, blood, and biologics are safe, effective, and available.
- ◆ The Center for Drug Evaluation and Research (CDER), which regulates the manufacture, labeling, and use of over-the-counter and prescription drugs, including biological therapeutics and generic drugs.
- ◆ The Center for Devices and Radiological Health (CDRH), which assures the safety, effectiveness, and quality of medical devices and radiation-emitting products, and fosters innovation in these products.
- ◆ The Center for Tobacco Products (CTP), which oversees implementation of the Family Smoking Prevention and Tobacco Control Act by setting standards, reviewing pre-market applications, requiring warning labels, and establishing and enforcing advertising and promotion restrictions.

**Office of Foods (OF)** provides all elements of FDA's Foods Program leadership, guidance, and support to achieve the Agency's public health goals. OF includes:

- ◆ The Center for Food Safety and Applied Nutrition (CFSAN), which ensures that the nation's food supply is safe, sanitary, wholesome, and honestly labeled, and that cosmetic products are safe and properly labeled.
- ◆ The Center for Veterinary Medicine (CVM), which regulates the manufacture and distribution of feed additives, drugs, and biologics intended for companion animals and animals used for food production, and evaluates the safety and efficacy of animal-based products, such as genetically modified animals.

**Office of the Chief Scientist (OCS)** provides strategic leadership, coordination, and expertise to support scientific excellence, innovation, and capacity to achieve FDA's public health mission. OCS includes:

- ◆ The National Center for Toxicological Research (NCTR), which provides scientific expertise to FDA; develops innovative methods and technologies to support FDA's mission; and helps disseminate regulatory science practices to countries seeking to develop science-based regulatory systems.

\* This list comprises FDA Offices and Centers with substantial involvement in global engagement. For a complete list of FDA Offices and Centers, see <http://www.fda.gov/AboutFDA/CentersOffices/default.htm>.

## FDA Has New Authorities to Ensure Food Safety

FDA can only realistically inspect a small percentage (less than 3 percent) of the enormous volume of food products arriving at U.S. ports of entry, making it crucial that the Agency focus on ensuring that food products meet U.S. standards *before* they reach the United States.<sup>9</sup> The Food Safety Modernization Act (FSMA), signed into law in January 2011, provides FDA with critical authorities to implement a significant new approach for protecting the safety and security of the U.S. food supply—one that promotes a

new level of accountability for all entities in the supply chain from farm to fork—regardless of where they are in the world.



Consumers around the world, not just in the United States, expect and demand safe food, no matter its source.

Michael Taylor, FDA Deputy Commissioner for Foods



## Medical Products

### U.S. Demand for Medical Products Has Grown Substantially Over the Past Decade

FDA regulates a wide variety of medical products:

- ◆ **Pharmaceutical products and components**, including brand-name and generic prescription drugs and over-the-counter remedies for both humans and animals, as well as other health-related products, such as sunscreens and fluoride toothpastes.
- ◆ **Biologics** (products typically made from living organisms), including human vaccines, blood and blood components, gene therapy, and tissues.
- ◆ **Medical devices**, from simple tongue depressors, surgical gloves, and dental amalgams to complex medical equipment—including in-vitro diagnostic products; cutting-edge diagnostic imaging equipment; artificial pancreases; robotically controlled surgical systems; and complex programmable cardiac pacemakers and implantable defibrillators.

U.S. demand for medical products grew substantially between the late 1990s and 2010, spurred in large part by the emergence of new medical technologies and services that were widely adopted by the U.S. health care system.<sup>10</sup> In recent years, this large U.S. demand has increasingly been met by imported products.<sup>11</sup> Since 2002, for example, imports of pharmaceutical products and biologics have more than doubled, and medical device imports have quadrupled.<sup>12</sup> Foreign-sourced pharmaceuticals now account for some 40 percent of the drugs consumed in the United States, and an astonishing 80 percent of the active ingredients in U.S.-consumed drugs are sourced from abroad.<sup>13</sup> With respect to medical devices, imports



now represent more than 35 percent of the U.S. medical equipment market.<sup>14</sup>

Globalization of the medical product industry presents regulatory challenges at every stage—from product development to final purchase and use by health care providers or consumers, as illustrated by the following three examples.

### Clinical Trials of New Medical Products Are Increasingly Conducted Abroad

All new medical products (drugs, biologics, and devices) must receive FDA review and clearance or approval before they can be marketed in the United States. As part of the premarket approval process, manufacturers must conduct clinical trials (scientific studies conducted with human subjects) to determine if the proposed product is safe and effective. FDA inspects clinical trial sites to ensure that participants

are protected and the trial is designed and executed to yield accurate, relevant data on the product.

Clinical trials are increasingly conducted abroad, often in nations with limited regulatory capacity. From October 2007 to September 2008, for example, clinical trials for medical products were conducted at nearly 6,500 foreign research sites and involved more than 230,000 subjects.<sup>15</sup> The increasing number of clinical trials conducted abroad adds to the complexities of FDA reviews of product applications.

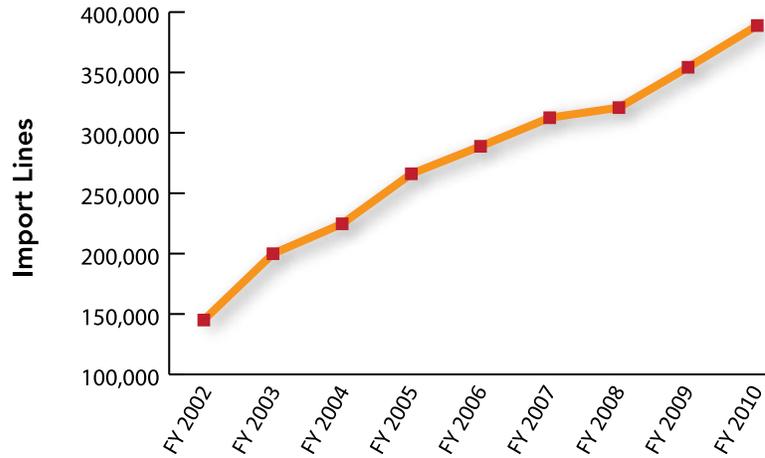
### Imported Medical Products May Pose Risks

Due to the high profit potential, imported medical products are vulnerable to economically motivated actions that can pose a significant risk to consumers. For pharmaceuticals, these risks apply equally to branded and generic drugs, and include economic adulteration and substandard/counterfeit/falsified products. With the proliferation of global commerce, many U.S. consumers can purchase pharmaceuticals electronically and more directly from foreign sources, increasing their potential exposure to these health risks.

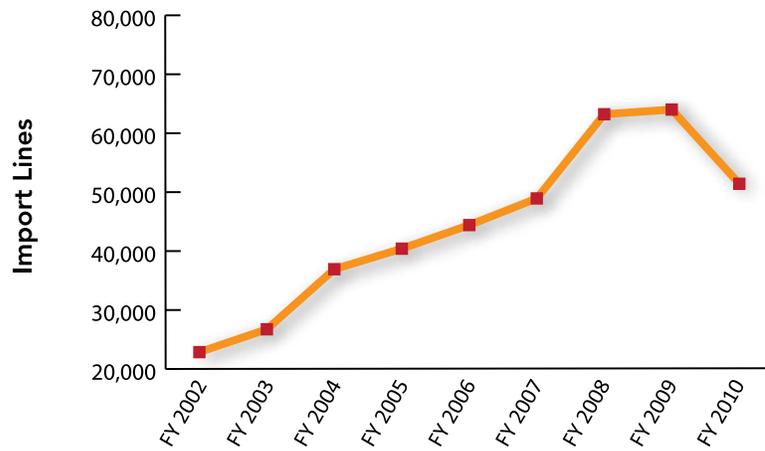
### Lack of Unique Identifiers for Medical Devices Poses Challenges

Many medical devices are sold in identical or nearly identical forms around the world, but are known by different trade names depending on the market. Most of these devices lack an internationally consistent “identifier” (e.g., a unique name or number assigned only to that product). When a regulatory authority discovers a problem with a medical device in one country, counterpart authorities in other countries find it difficult or impossible to know whether medical devices used in their countries are comparable or identical to the defective product. The inability to make a match significantly impairs the ability of FDA and other authorities to warn medical professionals and consumers about potential dangers.

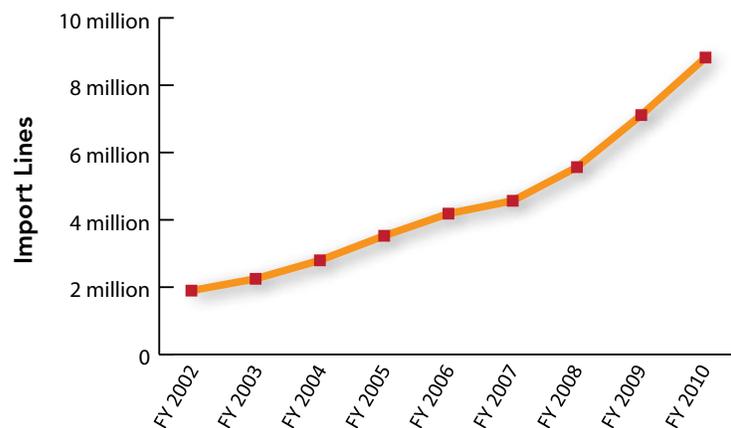
### Pharmaceutical Imports Have More Than Doubled Since 2002



### Biologics Imports Have More Than Doubled Since 2002



### Medical Device Imports Have Increased Over 450 Percent Since 2002



Source: Veneziano, D. 2011. *Import Stats FY 2002-2010*. U.S. FDA, Division of Import Operations and Policy, Office of Regulatory Affairs, Washington, DC.

## Tobacco Products

Unlike food and medical products, tobacco products, including cigarettes and smokeless tobacco, are inherently unsafe. Their use takes a deep toll on U.S. public health and economy, resulting in around 443,000 deaths and \$193 billion in medical costs and lost productivity each year. More than 8.5 million Americans have chronic illnesses related to smoking, and adults who smoke cigarettes die 14 years earlier on average than non-smokers. Virtually all new users of tobacco products are under 18, and one in four U.S. high school students report using tobacco.<sup>16, 17</sup>



FDA received authority to regulate tobacco products in June 2009, with passage of the historic Family Smoking Prevention and Tobacco Control Act. The Agency promptly established the Center for Tobacco Products to protect public health and reduce tobacco use by minors by regulating the manufacture, marketing, and distribution of tobacco products. CTP's work includes setting performance standards, reviewing premarket applications for tobacco products, requiring new warning labels, and restricting the advertising and promotion of tobacco products.

In its initial years, CTP has focused on establishing the scientific foundation and regulatory framework for regulating tobacco products in the United States. In addition to many domestic initiatives, this work involves reaching out to and building relationships with tobacco regulators around the world who face similar challenges in protecting the public from the risks and consequences of using tobacco products. CTP officials meet frequently with counterparts individually and at international forums, and are working, in partnership with the World Health Organization (WHO) and others, to lay a foundation for a global coalition of tobacco regulators who can share information on best practices, ideas, and resources for effective tobacco regulation.



## Strategies for Global Engagement

With the growing global economy, the risks of imported products are increasingly shared by countries around the world. Now more than ever, effective public health protection requires a range of stakeholders, including government agencies, industries, academia, non-governmental organizations, and scientific communities, to work together in partnership toward a single goal: protecting public health worldwide.

In response to these challenges, FDA has embraced a wide variety of strategies that increase its engagement in the global public health community, integrating the Agency's knowledge of how products are developed, manufactured, and delivered worldwide, and its ability to ensure that the imported products available to U.S. consumers are safe and effective. These strategies include:

- ◆ **International Offices and Posts.** FDA's international offices and posts build strong, sustained partnerships with their counterparts abroad; serve as a portal for other countries to the Agency; collect and leverage local and regional knowledge; and provide a platform for inspection of foreign facilities.
- ◆ **Strengthening Regulatory Capacity.** The capacity of governments to manage, assess, and regulate products within increasingly complex supply chains is a fundamental factor affecting product safety and efficacy. FDA is working strategically with a range of countries to provide information, tools, training, and exchange programs that contribute to building or strengthening regulatory capacity.

- ◆ **Harmonizing Science-Based Standards.** FDA and its counterparts around the world have been working for years to harmonize regulatory standards. As a result, participating countries increasingly share a common foundation of science-based goals for product safety, quality, and efficacy.
- ◆ **Leveraging Knowledge and Resources.** With the challenges of today's global marketplace, regulatory authorities must utilize their finite resources strategically and efficiently. Arrangements to share knowledge and information, and collaborative partnerships for regulatory decision-making, offer powerful and mutually beneficial leveraging tools for FDA and other countries and organizations.
- ◆ **Risk-Based Monitoring and Inspection.** To make the most of its resources for monitoring and inspecting imported products, FDA is developing innovative strategies and tools that take advantage of the latest developments in science, engineering, and information technology. One example is FDA's Predictive Risk-Based Evaluation for Dynamic Import Compliance Targeting (PREDICT) system, which helps screen the millions of imported food and medical products that enter the United States each year to rapidly identify those that pose the greatest risk to public health.
- ◆ **Global Surveillance, Preparedness, and Emergency Response.** Working with partners in the United States and around the globe, FDA helps monitor, prepare for, and respond to global public health challenges, such as international pandemics or widespread distribution of tainted FDA-regulated products.
- ◆ **Advancing Regulatory Science.** The rapid advances in science and technology that have contributed to the pace of globalization offer tremendous promise for promoting and protecting the safety, quality, and security of FDA-regulated products. FDA is actively engaging with global partners to harness scientific developments and pool products, resources, and brainpower to support science-based regulatory decision-making and pursue the best possible public health solutions.

In addition, as described in FDA's 2011 special report, *Pathway to Global Product Safety and Quality*,<sup>18</sup> the Agency is working to transform itself over the next ten years from a domestic agency operating in a globalized economy to a truly global agency fully prepared for the regulatory pressures of globalization. Toward that end, the Agency will be collaborating closely with its foreign counterparts to assemble global coalitions of regulators dedicated to building and strengthening a worldwide product safety net, including a global data information system they can use to proactively share real-time information and resources across markets. To achieve a true and lasting paradigm shift, FDA will be engaging stakeholders in a process that will unfold over the next several years.





# INTERNATIONAL OFFICES AND POSTS

When several imported food and medical products caused a series of U.S. public health crises in 2007 and 2008, it became clear that FDA's lack of an overseas presence impaired the Agency's ability to respond quickly and efficiently. FDA, with support from the U.S. Congress, reacted swiftly by establishing international offices and posting staff in strategic locations around the world. As of 2011, these include:

- ◆ **China Office**, which consists of posts in Beijing, Shanghai, and Guangzhou.
- ◆ **India Office**, which consists of posts in New Delhi and Mumbai.
- ◆ **Latin America Office**, which consists of posts in San Jose, Costa Rica; Santiago, Chile; and Mexico City, Mexico.
- ◆ **Europe Office**, which consists of posts in Brussels, Belgium; London, United Kingdom; and Parma, Italy.
- ◆ **Asia-Pacific Office**, located at FDA headquarters.
- ◆ **Sub-Saharan Africa Post**, located in Pretoria, South Africa.
- ◆ **Middle East and North Africa Post**, located in Amman, Jordan.

Operating under FDA's OIP, these offices and posts allow FDA to have a presence around the world. FDA staff work closely with their foreign regulatory counterparts, the industry and scientific/academic communities in-country, as well as with other U.S. Government agencies stationed abroad, to perform functions essential to FDA's ability to protect U.S. consumers. These include:



Kathleen Sebelius, Secretary of the U.S. Department of Health and Human Services (HHS), leads a delegation of FDA and other HHS agency representatives to meet with Indian Government officials, industry, and other Indian stakeholders in January 2012.

- ◆ Building linkages and trust with foreign counterparts.
- ◆ Developing a knowledge base of the regulatory, public health, cultural, economic, security, and geopolitical landscape.
- ◆ Monitoring local economic developments and natural events that may affect the quality and availability of food and medical products bound for the United States.
- ◆ Identifying and championing system-based approaches and initiatives of priority and mutual benefit to the United States and the host country/region.
- ◆ Serving as the face and voice of FDA in-country, connecting FDA experts with relevant stakeholders to increase their understanding and knowledge of the Agency's policies, regulations, and guidance for imported products.



## China Office



FDA opened its first international office—in China—in November 2008. China was of particular interest to FDA because it is a major and rapidly growing source of FDA-regulated imports. In 2008, for example, the United States imported over \$5 billion of food products from China (approximately 6 percent, in dollar value, of total U.S. food imports that year);<sup>19, 20</sup> almost \$700 million of pharmaceutical products;<sup>21</sup> and more than \$3 billion of medical devices.<sup>22</sup> Comprising three posts (in Beijing, Shanghai, and Guangzhou), the Office includes experts in food, drugs, and medical devices.

The opening of FDA's China Office was a critical milestone in the new era in U.S.–China cooperation on the safety of food, animal feed, and medical products.

Chris Hickey, Director, FDA China Office

### Strengthening Regulatory Capacity

FDA's China Office collaborates with its counterparts to build regulatory capacity and share best practices—for example, by facilitating FDA training in important regulatory areas, including low-acid canned foods,<sup>23</sup> aquaculture, good clinical practices, and quality systems.

The China Office has also collaborated with FDA Centers and Peking University to establish a world-class graduate degree program in pharmaceutical engineering management. This model program trains future leaders in China's pharmaceutical industry, while accelerating modernization of the industry itself.



New York City's Chinatown district is one of many places across the United States where consumers can purchase food imported from China.

## A New Era in U.S.–China Cooperation

FDA and its Chinese counterparts formalized a new era of cooperation in December 2007, when the United States and China signed two precedent-setting memoranda of agreement to enhance the safety of food, drugs, medical devices, and animal feed traded between the two countries.<sup>24</sup>

Under these legally binding agreements, the United States and China have agreed to notify one another as soon as they discover a circumstance, such as a product recall, that could endanger public health. In addition, Chinese regulators will require registration of products exported to the United States and work toward a system to certify that these products meet FDA standards before they are exported.<sup>25</sup>

These agreements—currently the only binding agreements FDA has with another regulator—have provided an important framework for FDA's China Office to enhance technical cooperation and information flow with its Chinese counterparts.

### In-Country Inspectors

The China Office includes several inspectors posted in Shanghai and Guangzhou. In addition to scheduled inspections, they can respond rapidly when needed to inspect high-risk facilities and in times of crisis—for example, when a safety issue is discovered with a Chinese-manufactured product. Since regulation of much of the food, drug, and device safety work in China is done at the local level, the FDA inspectors take time to build strong relationships with local Chinese regulators. They also help train Chinese regulators in good inspection practices, conduct outreach to Chinese industry, and participate in public forums.

(by volume) and the eighth largest food exporter (by volume) to the United States.<sup>26, 27</sup> Also, with a diverse population, a highly skilled work force, and favorable economic conditions, India has become an increasingly attractive location for clinical trials. As a result, the value of India's clinical trial market more than tripled between 2002 and 2008.<sup>28, 29</sup>

FDA's India Office consists of two posts, in New Delhi and Mumbai, staffed by experts in drugs, devices, and food, and by inspectors. The India Office has been working to build and sustain productive relationships with its counterparts to address regulatory issues of mutual interest and rapidly coordinate responses to emergent or other urgent public health situations.

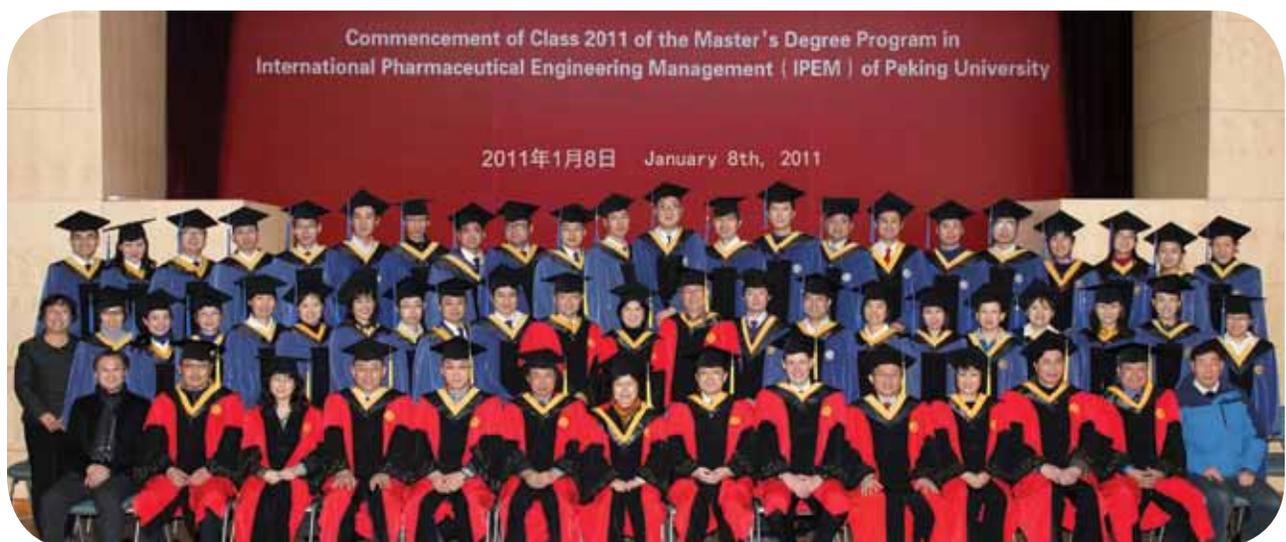


## India Office

FDA opened its India Office in November 2008. With a rapidly growing economy, India has been emerging as a key U.S. trading partner. For example, in 2009, India was the fourth largest drug exporter

### Strengthening Regulatory Capacity

Working with its Indian counterparts and with FDA Centers and ORA, the India Office identifies priorities for building capacity and technical collaboration, and partners with the Indian Government and industry stakeholders, where possible, to address these



Commencement of the Peking University 2011 Master's Degree Program in International Pharmaceutical Engineering Management.

priorities. For example, in response to Indian regulators' request for a multi-year "train-the-trainers" program on good clinical practices/clinical research inspections, FDA's India Office and experts worked to adapt a program for delivery in India.<sup>30</sup> As a direct result, the Indian drug regulatory authority now certifies inspectors for clinical trial inspections, as well as trainers to expand future capacity.

### In-Country Inspectors

FDA's India Office includes five inspectors posted in Mumbai who receive regular inspection assignments from FDA headquarters covering the full spectrum of FDA-regulated products. The in-country inspectors can also respond rapidly when needed to meet a short timeframe (such as a regulatory deadline) or to inspect high-risk facilities when a safety issue is discovered with an Indian-manufactured product. For example, the India Office was able to send investigators to inspect an Indian facility within one working day after a pharmaceutical product manufactured in the facility was voluntarily recalled from U.S. commerce by the U.S. distributor due to contamination concerns. The investigators identified several Good Manufacturing Practices (GMP) violations, and the inspection results enabled FDA to place the manufacturer on import alert until the violations were corrected.

Since most of the food, drug, and device safety work in India is regulated at the local level, FDA in-country inspectors set aside time to interact with their local counterparts and build strong relationships with state-based regulators. They also participate in public forums hosted by Indian manufacturing associations to educate manufacturers about FDA requirements and help them improve their ability to meet U.S. requirements.



## Latin America Office

FDA's Latin America Office (with posts in San Jose, Costa Rica; Santiago, Chile; and Mexico City, Mexico) opened in April 2009. The Office covers 44 countries and territories in Mexico, Central America, South America, and the Caribbean—a large and geographically varied region, with a diverse range of regulatory systems and product issues. FDA staff in Latin America have traveled extensively to meet with relevant stakeholders—including government representatives from the regulatory, health, agriculture,



India provides about a quarter of the spices, oils, and food colorings used in the United States.<sup>31</sup>

commerce, and trade sectors; industry and trade associations; development organizations; multilateral organizations; and academia—many of whom have expressed a strong appreciation for FDA's presence. Key activities include increasing knowledge and information about FDA regulations, guidelines, and requirements; building FDA's knowledge base about regional systems and practices; and identifying the most strategic areas for collaboration, capacity building, and harmonization of standards and practices. Though FDA inspectors are not part of the Latin America Office per se, FDA posts create a foundation for FDA food safety and surveillance inspections by providing advance liaison with industry and regulatory authorities.

### Strengthening Regulatory Capacity

Given the diversity of FDA-regulated products imported from Latin America, the strategic use of limited resources is critical. To that end, the Latin America Office has focused on programs designed to foster broad dissemination of key information. For example, for many of its "train-the-trainer" programs, FDA's Latin America Office invites officials to participate who have the capacity and authority to widely disseminate training in their home countries. A number of FDA documents have been translated into Spanish to expand FDA's reach. Training and guidance on food labeling has been a priority topic to help ensure that exports comply with FDA requirements for entry into the United States.

Local governments and health organizations in the region have expressed a significant interest in strengthening their capacity to perform food and clinical research inspections comparable to FDA inspections. Future work to build inspection capacity will help increase FDA's confidence in using data from inspections conducted by local authorities.



## Europe Office

FDA's Europe Office enhances a longstanding tradition of cooperation with European regulatory authorities on public health issues of mutual importance. The Office, which covers the European Union (EU) and individual countries that are not EU members, such as Switzerland and Norway, facilitates progress on many joint European–U.S. projects spanning the full spectrum of FDA-regulated products. Shared interests, well-honed relationships, and comparable regulatory standards provide a rich foundation for productive partnerships and leveraging of resources to benefit public health on both sides of the Atlantic.

FDA opened its Europe Office in Brussels, Belgium, in May 2009. Under reciprocal arrangements, FDA staff members are also based at the European Medicines Agency (EMA) in London, United Kingdom, and the European Food Safety Agency (EFSA) in Parma, Italy, while EMA and EFSA staff are posted at FDA headquarters in the United States.

FDA's Europe Office maintains an active bilateral relationship with national regulatory authorities (NRAs) throughout Europe, and has confidentiality commitments with a number of European authorities and countries, including the European Commission, France, Germany, Ireland, Italy, and the Netherlands.

### Leveraging Inspection Resources

With comparable rigor in FDA and EMA inspections, significant opportunities exist for the two agencies to leverage their inspection resources. FDA and EMA have been exploring this potential through a series of activities. They have observed each other's inspections and jointly inspected manufacturing sites in the United States and the EU. Through this work, FDA and EMA are building a foundation for understanding, trust, and data-driven decisions.

### Parallel Scientific Advice

FDA and EMA have been collaborating in providing parallel scientific advice to drug sponsors who want to submit a new drug application for review in both U.S. and European markets. The voluntary process is initiated at the request of the sponsor early in the product development phase. The agencies agree to look at the sponsor's application in parallel and provide advice to the sponsor at the same time. The sponsor submits the same briefing package to both agencies, who share their responses with one another. FDA and EMA meet jointly with the sponsor on what may be needed for approval, while also learning from each other's



EMA–FDA interactions contribute to the availability of safe and effective new medicines, as early as possible, with data relevant to all regions.

Hilde Boone, European Medicines Agency Liaison to FDA

concerns. Though FDA and EMA issue separate responses, sponsors benefit from increased efficiency and opportunities for alignment, while the agencies benefit from communication and interaction and gain increased understanding in case of divergent outcomes.

### Product Evaluation and Surveillance

FDA and EMA scientists leverage their knowledge by participating in regular discussions and information exchanges about ongoing industry marketing applications for products in areas of common interest, such as oncology, vaccines, advanced therapies, pharmacovigilance, blood products, gene therapy, biomarkers, pediatric medicines, veterinary products, and orphan drugs for rare diseases. Discussions include data interpretation, product approval requirements, and post-marketing studies. In many of the topic areas, FDA and EMA scientists are among only a small number worldwide working on these issues, making these discussions particularly critical to inform the agencies' decisions about the marketing applications received. FDA and EMA also hold extensive ad hoc exchanges on other product-specific review and safety issues, and provide advance notice of important regulatory decisions.

### Food Safety Comparability

FDA's Europe Office has made invaluable inroads on several food issues where the United States and the EU have differing perspectives. For example, the FDA and the EU have been assessing the comparability of their two food safety systems to lay the groundwork for future comparability work under FSMA.



## Asia-Pacific Office

FDA's Asia-Pacific Office, based at FDA's headquarters, is responsible for a broad area comprising Canada and the 29 countries of the Asia-Pacific region, excluding China and India. These countries are diverse, ranging from tiny island nations to major world economies. They include countries with highly developed regulatory systems and longstanding FDA

## Pilot Project to Compare the New Zealand and U.S. Food Safety Systems

FDA has a longstanding, collaborative working relationship with its counterpart agency in New Zealand, the New Zealand Food Safety Authority (NZFSA), which merged with New Zealand's Ministry of Agriculture and Fisheries in 2010. Recently, NZFSA participated in a comparability pilot project conducted by FDA. The project involved extensive review by FDA of New Zealand's food safety system to determine whether it provides a comparable level of public health protection to the U.S. food safety system. The project results are being assessed. If the outcome shows positive comparability, this may enable FDA and New Zealand to leverage their food safety resources in the future. The comparability review will also form the basis for renewing Memoranda of Understanding between the two countries regarding New Zealand exports of seafood, shellfish, and non-Grade A dairy products to the United States.



The globalization trajectory among nations is clearly toward greater collegiality, collaboration, transparency, and data-sharing, leading to a greater reliance on each other.

Paul Seligman, Director, FDA Asia-Pacific Office

relationships (such as Canada, Japan, Australia, and New Zealand), as well as emerging economic powers (such as South Korea and Singapore).

FDA has worked multilaterally with the Asia-Pacific Economic Cooperation (APEC), an intergovernmental forum comprising 21 member economies in the Asia-Pacific region, to provide advanced Good Clinical Practices (GCP) inspection training; work towards strengthening food safety systems; and combat falsified or counterfeit medicines. In 2011, FDA Commissioner Margaret Hamburg led the U.S. delegation to the third meeting of APEC's Food Safety Cooperation Forum, which was hosted by the United States. FDA is also a partner with the Food Safety Cooperation Forum's Partnership Training Institute Network, which strengthens capacity building in food safety by engaging the food industry and academic food safety experts with the regulators.



## Middle East/ North Africa Post

FDA's Middle East and North Africa (MENA) post, located in Amman, Jordan, covers 20 countries in the region with varying levels of regulatory maturity. The post, which opened in June 2011, is becoming increasingly important as the number of FDA-regulated

product lines exported to the United States from the region continues to rise.

Through its Senior Regional Advisor for the Middle East and North Africa, FDA is working to build collaborative relationships with its counterparts and support implementation of preventive, risk-based approaches to ensuring product safety and quality. For example, FDA's OIP recently helped Jordanian counterparts better understand the Agency's food packaging regulations as a possible model for developing Jordanian food packaging regulations; and FDA sent experts to Saudi Arabia to explain FDA medical device regulations and to discuss potential pathways for the Saudi Food and Drug Authority to establish its own in vitro diagnostic laboratory. The MENA post is also engaging with industries to help them understand and comply with FDA's import requirements.

As a trading crossroads, the MENA region often serves as an interim destination (e.g., for labeling and packaging) for products bound for the United States. FDA's Senior Regional Advisor for the Middle East and North Africa is working with counterparts to support development of mechanisms that will better enable FDA to identify at U.S. borders adulterated and misbranded products shipped from the region.

FDA is also providing training and information exchange to strengthen regulatory capacity. For example, OIP hosted a conference in Cairo, Egypt, in 2010 to create an opportunity for food regulators to share their experiences with the elements and challenges of strong food safety systems. In 2012, FDA will provide GCP training for regulators of clinical trials. In addition, FDA is translating key documents into Arabic (the major language of the region) and making them available to regulatory counterparts and industry to help ensure the safety of FDA-regulated foods and medical imports from the region.





## Sub-Saharan Africa Post

FDA's Sub-Saharan Africa (SSA) post, which opened in Pretoria, South Africa, in June 2011, covers the 48 countries of Sub-Saharan Africa. While many of Africa's developing economies continue to struggle, some are poised to take advantage of import/export initiatives.

In prior years, staff operating out of FDA headquarters had built a framework of relationships and sharing with several African countries through information exchange and training. With its SSA Post, the Agency can now reach out to more Sub-Saharan African countries, particularly those with limited government public health staff.

The SSA post will leverage its resources in several ways. For example, African countries have bound together in multiple regional blocks, known as Regional Economic Communities (RECs), to pool their resources and expertise and work towards mutual development and economic goals. The SSA post plans to mirror this approach by working under the umbrella of the REC Secretariats; targeting country blocks; and focusing on collaborative efforts designed for maximum benefit and impact.

The SSA post will partner with other U.S. agencies at the U.S. Embassy in Pretoria to build on the relationships these agencies have already established with government counterparts in the region. During the initial months of the SSA post, the Senior Regional Advisor for Sub-Saharan Africa has met with U.S. Government colleagues and regional intergovernmental organizations to develop relationships; understand their priorities; and consider potential areas for mutual support, collaboration, and synergy.



Reviewing case materials at GCP training in Botswana in October 2010.

## The President's Emergency Plan for AIDS Relief (PEPFAR)

FDA supports the U.S. Government's PEPFAR program, the largest commitment by any single nation to combat a disease internationally.<sup>32</sup> One of the program's key areas of focus is to make antiretroviral treatment—currently the most effective treatment for AIDS—available to persons living with AIDS. Antiretroviral treatment, which typically involves administering at least three drugs, dramatically reduces the number and severity of HIV-associated illnesses, improving both the duration and quality of life for AIDS patients.

Under PEPFAR, FDA's CDER has been responsible for coordinating a process whereby generic antiretroviral medicines, including formulations for children, have received approvals certifying that they meet the safety and quality standards of products in the United States. Purchasers of products under the PEPFAR program use these "tentative" approvals to guide their purchases. FDA is now working collaboratively with industry and other health organizations to promote faster approval of these medicines by the regulatory authorities in PEPFAR countries so they can reach AIDS patients without delay.

By streamlining the decision process, these approvals save many millions of dollars per year and enable millions of people in PEPFAR countries, including those in Africa and Asia, to receive life-preserving therapies for HIV/AIDS. As of September 30, 2010, more than 3.2 million men, women, and children worldwide had received anti-retroviral treatment supported by PEPFAR.<sup>33</sup>

With many clinical trials now taking place in the Sub-Saharan Africa region, strengthening regulatory oversight of these trials is an important FDA priority. FDA conducted GCP inspection training for the region in 2010 and 2011, with 11 nations participating, and advanced GCP training in 2011, with 13 nations participating. South Africa, which has had well-conducted trials for decades, has been participating to assist neighboring countries with little experience.



# STRENGTHENING REGULATORY CAPACITY

**R**egulatory capacity is the ability of government authorities to ensure the availability of safe, high quality food, medical, and other FDA-regulated products by effectively performing critical regulatory functions—including product review, registration, licensing, inspection, laboratory testing, and post-market surveillance.

With substantial U.S. consumption of imported food and medical products, the ability of other countries to ensure the safety and quality of products they export has direct relevance to U.S. public health. A vital element of FDA's global engagement portfolio, strengthening regulatory capacity promotes the safety of imported products and improves the control of diseases before they reach U.S. borders.<sup>34, 35</sup> In addition, stronger regulatory capacity abroad significantly improves the health and quality of life for individuals and communities in the developing world, and helps reinforce and secure public and private investments in the development of new drugs and vaccines, as well as agriculture and food production.<sup>36</sup> Capacity building activities can take place at multiple levels: a country's regulatory environment, its organizations and institutions, and/or with individuals in the relevant scientific and regulatory communities.<sup>37</sup>



By helping countries build their regulatory capacities, we strengthen their power to improve the safety and value of goods their own people consume, while also building confidence in the imports they send to the United States.

Margaret Hamburg, FDA Commissioner



## Transferring Regulatory Knowledge and Information

OIP works with all of FDA's Centers and Offices in the area of capacity building. These efforts involve transferring essential information, knowledge, tools, and strategies to other nations so that they can apply and adapt them to develop and strengthen their own regulatory infrastructures. The work generally takes the form of education/training, dissemination of materials, and the translation of training modules and documents in scientific, technical, regulatory, and inspection areas. The following examples highlight a range of strategies that FDA employs to help strengthen regulatory capacity.

### FDA Forums for International Regulatory Authorities

FDA Centers host frequent forums where regulatory counterparts from around the world can exchange information, build collaborative relationships, and deepen their understanding of FDA operations and regulatory requirements for medical products:

- ◆ **Drugs.** Since 2005, CDER has organized the "CDER Forum for International Drug Regulatory Authorities" twice a year, in April and October. The forums provide an opportunity for foreign regulators to learn about FDA and its drug review process, and to exchange drug regulatory information. Collectively, almost 500 international colleagues from more than 70 countries have attended the 13 forums CDER has held through October 2011.



Participants at the October 2011 CDER Forum for International Drug Regulatory Authorities.

- ◆ **Medical Devices.** Since 2009, CDRH has hosted two forums a year to provide an opportunity for medical device regulators to build collaborative relationships; exchange regulatory information and perspectives; and receive basic and advanced training on FDA-regulated medical devices and radiation-emitting products.
- ◆ **Biologics.** Starting in 2008, CBER has conducted a recurring seminar for foreign regulators on FDA regulation of biologics.

#### Online Educational Tools

- ◆ **CDER World.** Interest among foreign regulators in learning about the science, technology, regulations, and processes CDER uses to protect public health has grown exponentially in recent years. To meet this demand, and the needs of foreign colleagues who are unable to attend CDER's Forums for International Drug Regulatory Authorities, CDER with OIP support recently developed a Web-based information compendium called "CDER World."<sup>38</sup> This compendium comprises information about how CDER carries out its mission, adapts to new legislative initiatives, and initiates directions in regulatory science to improve public health. CDER World will grow and evolve as more modules are added over time.
- ◆ **CDRH Learn.** After developing online training modules for internal FDA use, CDRH learned that foreign regulators and device manufacturers also found them valuable. Accessible on FDA's website as "CDRH Learn,"<sup>39</sup> this comprehensive, interactive educational tool comprises a series of self-paced training modules covering a wide variety of topics on medical device and radiological

health regulation—from FDA's authority to CDRH's premarket review, postmarket surveillance, and enforcement programs. To expand the global reach, OIP and CDRH collaborated to translate the modules into Mandarin and Spanish in 2010 and 2011.

- ◆ **CBER Web-Based Biologics Seminar.** CBER maintains an online educational tool on FDA's website<sup>40</sup> to provide regulators around the world with ready access to information on U.S. regulatory oversight of biological products. This information mirrors that presented during CBER's recurring seminars for foreign regulators, amplifying the global reach of this information. Users can email CBER with questions once they complete the online seminar.

#### International Scientist Exchange Program

In 2009, FDA's NCTR established the International Scientist Exchange Program (ISEP). ISEP builds global regulatory science capacity by training students, regulators, and academicians from developing countries. Through intensive hands-on research and mentorship onsite at NCTR in Jefferson, Arkansas, participants learn concepts, skills, and techniques essential to five core competencies in regulatory science: laboratory safety, study design, research ethics, bioinformatics, and data integrity. The goal is to provide participants, selected in part for their leadership potential, with sufficient training to successfully utilize these competencies when they return to their respective countries. Participants have included:

- ◆ Three scientists from China's State Food and Drug Administration, who spent more than four months at NCTR applying bioinformatics



technologies to regulatory data so they could return to facilitate development of a bioinformatics infrastructure in China.

- ◆ A scientist from the University of São Paulo, Brazil, who spent a year collaborating in a community-based biomedical participatory research project so she could apply this research approach in Brazil to support the protection of ethnically diverse populations.
- ◆ A mathematical statistician from Korea University, South Korea, who trained in toxicogenomics, a new discipline to assess the health risks of drugs. This research has relevance to regulatory decision-making in a number of countries, including the United States and South Korea.

### Joint Institute for Food Safety and Applied Nutrition (JIFSAN)

FDA's CFSAN, as an integral component of FDA's foods program, leverages part of its international capacity building efforts with the University of Maryland's JIFSAN to:

- ◆ Conduct in-country food safety training programs to build global capacity (e.g., Good Agricultural Practices).
- ◆ Participate in APEC's Partnership Training Institute Network to strengthen food safety capacity.
- ◆ Provide food safety risk analysis training to enhance the global use of risk analysis principles.
- ◆ Provide laboratory hands-on training through the International Food Safety Training Laboratory at JIFSAN.

### FDA Participation in Regional Capacity Building in Africa

CBER serves as a mentor within the African Vaccine Regulators Forum (AVAREF). Established by WHO in 2006, AVAREF acts as an ad hoc scientific advisory body to help NRAs in African countries develop and enhance their capacity to:<sup>41</sup>

- ◆ Review clinical trial authorizations and monitor vaccine clinical trials that foreign companies are proposing to conduct in their countries.
- ◆ Assess vaccine clinical data and product quality to determine whether to license vaccines for use in their country.

AVAREF provides a safe, secure environment for NRAs to discuss concerns and ask questions of experts and colleague regulators. For instance, when a manufacturer proposes conducting clinical trials in several African countries, NRAs can jointly discuss the protocol within AVAREF. CBER experts may help mentor NRA review of the protocol, including suggesting questions to raise about the protocol to help ensure that the trials will protect participants and meet appropriate standards for quality.



## Catalyzing Regional and Global Networks

FDA's systems-strengthening activities include support for development of information networks that can help strengthen capacity in different countries and organizations. These tools facilitate timely exchange of regulatory data, approaches, and tools, and strengthen the ability of organizations to better prevent, detect, assess, and respond to potential public health issues associated with food and medical products. For example:

- ◆ **Medical Products "Information Hub" for the Americas.** FDA is supporting the Pan American Health Organization (PAHO) in developing an "information hub."<sup>42</sup> This tool will help build capacity for effective regulation of medical products by making information about regulatory authorities, products, and the associated regulatory landscape in the Americas readily available.
- ◆ **WHO Drug Information Platform.** FDA, the WHO Secretariat, and WHO member states are working together to construct a global surveillance and monitoring system to combat substandard/counterfeit/falsified medicines. FDA and other WHO member states are working together to construct a sound evidence base that will underpin planning and implementation of policies and programs to tackle this global threat, ultimately benefiting patients and consumers in the United States and abroad.
- ◆ **Antimicrobial Resistance Information Exchange.** FDA and WHO are collaborating to support a worldwide exchange of information and expertise in matters concerning resistance of foodborne pathogens and disease to anti-microbial treatments (known as anti-microbial resistance, or AMR). By providing rapid access to AMR data worldwide, such a network will strengthen AMR

decision-making and help build capacity for laboratory-based AMR surveillance in developing regions.<sup>43</sup>



- ◆ **Global Collaboration on Veterinary Drugs.** FDA collaborates with the World Organization for Animal Health (OIE) to raise awareness among foreign regulators about the importance of science-based safety standards for veterinary drugs, and strengthen their capacity to adopt and implement such standards at the country level to improve animal health and welfare and increase the safety of food of animal origin. FDA's CVM was recently designated as an OIE Collaborating Centre in recognition of its expertise in veterinary drug regulatory programs.



## International Tobacco Regulators' Conference

In November 2011, FDA's CTP and OIP held an international conference for tobacco regulators. Co-sponsored with WHO's Tobacco Free Initiative, the International Tobacco Regulators' Conference was attended by regulators from 22 countries that are actively regulating tobacco products or considering doing so.

The conference provided a unique opportunity for participants to learn from one another and engage in robust dialogue about successes and failures in global tobacco regulation; specific tobacco control initiatives; and opportunities for international collaboration. Conference participants agreed to establish an informal network of tobacco regulators from around the globe to share information and collaborate on tobacco control efforts.



## Strategic Investment of Capacity Building Resources

FDA's assistance in strengthening foreign regulatory capacity is often sought by other governments and public health organizations. The need for capacity building is compelling, given the large number of countries that have limited or under-resourced regulatory systems for ensuring the safety and quality of FDA-regulated products they export to the United States. Consequently, OIP has been working collaboratively with FDA Centers and Offices to ensure that the Agency's capacity building resources are deployed strategically. To support strategic resource use, FDA has invested in several baseline studies to learn where FDA investments can have maximum impact in strengthening regulatory decision-making:

- ◆ **International Regulatory Capacity Study.** At FDA's request, the National Academy of Sciences' Institute of Medicine (IOM) is working to characterize the regulatory landscape and the essential elements of regulatory systems in developing countries within the broader development assistance and economic development context. This work includes assessing where the greatest potential exists for FDA to facilitate strengthening regulatory systems in developing countries and how the Agency can partner with other relevant organizations (e.g., bilateral donors, development banks, foundations, academia, industry and non-governmental organizations) to leave a sustainable "footprint" that benefits the countries involved and the United States.<sup>44, 45</sup>
- ◆ **Global Training Landscape Study.** FDA has begun a global assessment of regulatory training institutions, capacities, and approaches. This study will help the Agency identify gaps in training; particular niches that FDA can uniquely fill; and areas where collaboration and synergies with other regulatory authorities and institutions could be explored.
- ◆ **Pharmaceuticals Systems Review.** Pharmacovigilance is the science relating to the detection, assessment, understanding, and prevention of adverse effects of medicines. In partnership with the U.S. Agency for International Development's Strengthening Pharmaceuticals Systems Program, FDA is analyzing pharmacovigilance capacities in Africa to better understand existing efforts and identify needs and opportunities for building capacity.



# HARMONIZING STANDARDS

**H**armonization involves the alignment among different nations of science-based regulatory standards for the quality, safety, and efficacy of imported and exported products. Food and medical products imported to the United States from countries that have adopted and successfully implemented internationally harmonized standards may be less likely to require FDA intervention or endanger U.S. public health. U.S. products, in turn, may be more readily accepted by other countries that use those same standards, as regulators abroad are assured that the products meet standards comparable to their own.

Harmonization helps governments realize efficiencies in developing, implementing, and enforcing standards. Industries also benefit from harmonization because they can focus on maintaining strict compliance with a single set of strong standards. By unifying the efforts of regulators and providing clear guidance to industry, harmonization benefits consumers through the availability of safer, more effective products.

FDA has been engaged over decades in a variety of formal harmonization efforts for many foods, drugs, medical devices, and other FDA-regulated products. In addition, FDA has led in the establishment of—and participates in—numerous international conferences and forums. These meetings provide opportunities for Agency staff to work informally with their international counterparts at all levels to identify, discuss, and address harmonization issues and associated regulatory and scientific challenges.

As of 2011, FDA has worked with regulators from more than 180 countries to develop food standards and guidelines, and with many countries to develop harmonized standards for pharmaceuticals, medical devices, and veterinary medicines. FDA also continues to work towards harmonization on a myriad of other related priorities, including product labeling and medical device identifiers. As science, technology, and society continue to evolve, new regulatory areas ripe for harmonization will emerge. The developing field of nanotechnology, for example, will require new, uniform standards to be developed and adopted around the world.



## Food Standards

FDA has participated in the work of the international, science-based Codex Alimentarius Commission (Codex) for more than 40 years. Codex develops science-based international food standards, guidelines, and codes of practice that protect the public health while ensuring fair practices in food trade. A joint program of the United Nations Food and Agriculture Organization (FAO) and WHO, Codex incorporates and builds on prior food standards work by national, regional, and international organizations. Codex comprises more than 180 countries, accounting for 97 percent of the world's population.



The process of working with scientists from 150 nations toward consensus on food standards development is dynamic and continually exciting. It's one of the most important things we do in CFSAN.

Camille Brewer, Director, International Affairs Staff, FDA Center for Food Safety and Applied Nutrition

## Codex has:

- ◆ Developed over **200** food standards for commodities and more than **40** codes of hygienic or technological practice.
- ◆ Evaluated over **180** pesticides and established more than **3,200** limits for pesticide residues.
- ◆ Developed more than **25** guidelines for contaminants.
- ◆ Evaluated over **1,000** food additives and more than **50** veterinary drugs.

## ICH Global Cooperation Group Members

- ◆ European Union, United States, Japan, Australia, Brazil, China, Chinese Taipei, India, Republic of Korea, Russia, and Singapore.
- ◆ Regional Harmonization Initiatives:
  - Asia-Pacific Economic Cooperation (APEC)
  - Association of Southeast Asian Nations (ASEAN)
  - East African Community (EAC)
  - Gulf Cooperation Council (GCC)
  - Pan American Network on Drug Regulatory Harmonization (PANDRH)
  - South African Development Community (SADC)

## Standards for Animal Health and Welfare

FDA's CVM supports the World Organization for Animal Health in its work to harmonize international standards and guidelines for animal welfare. CVM was recently designated as an official OIE Collaborating Centre, providing an important mechanism for CVM to offer its expertise to improve global capacity for animal disease prevention, detection, and control.

Codex's work covers foods and food-related products, and issues such as labeling, food additives, nutritional supplements, and pesticides and veterinary medicines that may affect food safety and quality. FDA has participated actively in Codex throughout its history. Over the course of its involvement, FDA has provided leadership in every one of Codex's 20-plus technical committees. As of October 2011, FDA's CFSAN and CVM provide the U.S. delegate or alternate delegate to 16 Codex committees.



## Pharmaceutical Standards

### International Conference on Harmonization

FDA is a founding member of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), which seeks to harmonize regulatory standards, processes, and procedures for the pharmaceutical industry. Established in 1990, ICH brings together drug regulatory authorities and pharmaceutical industry experts of the United States, European Union, and Japan. Additional participants, as observers, include WHO, Canada, and Australia.

Through its Global Cooperation Group, ICH has involved countries and regions with a history of implementing ICH guidelines and/or where major drug production and clinical research is conducted. In 2008, ICH further expanded the involvement of non-ICH countries by establishing the Global Regulators Forum, a yearly regulators-only meeting to promote an understanding of ICH guidelines, share expertise and best practices for implementing guidelines in non-ICH countries, and identify training and capacity needs.

ICH has developed a set of harmonized guidelines to help ensure drug safety and quality, while streamlining the development process for new drugs and the regulatory assessment of new drug applications. As of July 2010, ICH had finalized more than 80 guidelines for quality, safety, efficacy, and other areas for adoption by ICH members and other interested countries.

CBER, CDER, and OIP participate in and contribute expertise to ICH guideline development efforts and other activities to advance global harmonization. FDA's CVM participates in a related Veterinary Conference on International Harmonization (VICH), which harmonizes standards for veterinary products.

### Standards for Pharmaceutical Inspections

In January 2011,<sup>46</sup> FDA was granted membership to the Pharmaceutical Inspection Cooperation Scheme (PIC/S). Using a cooperative approach,

the 39-member PIC/S, comprised of regulators from around the world, pursues the international improvement and alignment of pharmaceutical inspections through information exchange, training, and harmonization of GMP standards and procedures among regulatory agencies.

### PAHO/WHO Collaborating Center for Biological Standardization

FDA's CBER is a PAHO/WHO Collaborating Center for Biological Standardization. In that capacity, CBER experts have contributed for many years to a range of global public health priorities that include providing expertise for developing WHO written standards and guidelines; undertaking collaborative studies for establishing WHO/ international biological reference preparations; and conducting research and testing to improve the standardization and control of biologicals used in humans.



ICH's major progress toward standardizing the information filed about the side effects of drugs makes it possible for FDA and our foreign counterparts to detect unexpected side effects much earlier than before.

Janet Woodcock, Director, FDA Center for Drug Evaluation and Research



## Harmonizing Regulatory Practices for Medical Devices

Medical devices run the technological gamut from the ancient to the ultramodern, from simple tongue depressors to complex programmable pacemakers and cutting-edge diagnostic imaging machines. With increased globalization, nations of vastly different levels of technological and regulatory advancement now produce and export these devices.

Since 1992, device regulators and industry from the European Union, United States, Canada, Australia, and Japan have worked collaboratively under the Global Harmonization Task Force (GHTF) to achieve greater uniformity in national medical device regulatory systems. For example, to promote global harmonization of approaches to regulating unique device identification (UDI) systems for medical devices, GHTF developed a framework (published in September 2011) that GHTF members are encouraged to follow when regulating these systems in their countries. Global harmonization



of UDI systems helps regulatory authorities respond swiftly and effectively to protect public health when a problem is discovered with a particular device.

Through liaison with other countries and involvement of observer organizations, GHTF also works to foster awareness and adoption by developing economies of GHTF documents and harmonized regulatory practices measures.

GHTF is aiming, by the end of 2012, to complete its regulatory documents and finalize a regulatory model that can be used by developing economies. During 2012 to 2013, GHTF will transition to a new format, the International Medical Device Regulators Forum (IMDRF), with a focus on maintaining the harmonized documents. IMDRF will comprise an expanded membership of regulatory bodies, observer organizations, and related communities that share a common goal of achieving greater international uniformity and convergence in regulatory practices for medical devices.

### Breaking Down Barriers to Timely Treatments

"Harmonization by Doing" is a U.S.–Japanese bilateral effort to develop harmonized standards for global clinical trials and address regulatory barriers that may delay timely medical device approvals. The process is a cooperative effort to move both Japan and the United States toward international regulatory harmonization. The two countries currently diverge in regulatory practices, but are willing to consider new ways of working to improve clinical trials. The effort aims to decrease the lag time between U.S. and Japanese product approval and ensure the early market availability of new treatment and devices for patients in both countries.



# LEVERAGING RESOURCES

**O**rganizations and agencies such as FDA leverage resources when they work in partnership to address issues of mutual interest and concern. By sharing knowledge, information, expertise, and work, partners create synergies and efficiencies that enhance their ability to achieve mutual public health goals—goals that would be difficult, often impossible, for a single organization to achieve alone.

FDA engages with a wide variety of organizations—including other government agencies, international organizations, regional consortiums, and non-government organizations—to leverage resources. Through effective engagement with selected partners, FDA expands its reach to protect public health with finite resources.<sup>47</sup> Similarly, FDA is placing increased reliance on audits by public and private third parties to help assure the quality and efficacy of products exported to the United States.



## Frameworks for Partnerships

Leveraging may take many forms, including informal arrangements or formal agreements. Some partnerships are bilateral, while others involve multiple organizations and/or nations. For each partnership, FDA may select from a variety of reciprocal arrangements, which can be expanded or refined over time as appropriate.

One type of arrangement is a confidentiality commitment, which allows FDA and a foreign counterpart to exchange non-public information with the assurance that the receiving agency will maintain the confidentiality of the information. Such agreements are an important public health tool, since a critical portion of



Resources are fully leveraged when countries have developed sufficient systems, relationships, and trust to rely on information and findings from their counterparts as completely as they rely on their own work.

Murray Lumpkin, FDA Senior Advisor and Representative for Global Issues

the information needed for regulatory decision-making and the protection of public health is pre-decisional, deliberative, and/or of a confidential nature. For example, FDA's collaboration with WHO, the European Union, and Canada, among others, to coordinate a response to the 2009 H1N1 outbreak, including sharing vaccine review and adverse event information, was possible because the partners held confidentiality commitments.<sup>48</sup> As of 2011, FDA had 50 confidentiality commitments with foreign counterparts.



## Foreign Facility Inspections

To help protect U.S. public health, investigators with FDA's ORA regularly travel around the globe to inspect foreign facilities involved in producing food and medical products intended for import to the United States. Inspections may be conducted for many reasons, including general surveillance and pre-approval inspections (to ensure that the facility is meeting GMP requirements), or in response to a specific concern with an import from a foreign facility. FDA's Centers work with ORA to identify risk and prioritize foreign firms

to inspect. When an inspection identifies significant violations, FDA may establish immediate controls to restrict the import of products from that facility until the violations are corrected. If a foreign facility refuses FDA's attempts to conduct an inspection, the Agency will restrict imports from that facility until an FDA inspection is conducted.

Because of the vast and growing number of foreign facilities, FDA does not have—nor will it—the resources to directly inspect all the higher-priority facilities at desired frequencies. For example, though ORA inspected more foreign facilities in FY 2011<sup>49</sup> than ever before in a single year, these inspections still account for only a small fraction of the more than 300,000 foreign facilities manufacturing or processing FDA-regulated products for the U.S. market. Leveraging resources with trusted partners offers a powerful way to address this gap and extend oversight to a higher number of facilities.

To leverage resources, the Agency establishes guidance and performs outreach with foreign industries to help them understand FDA requirements, and with foreign regulatory counterparts to help them build capacity in their country. Where confidentiality commitments allow, ORA collaborates with foreign regulatory counterparts to share laboratory and inspection information. Under the 2011 Food Safety Modernization Act, FDA is studying how regulatory controls and inspectional oversight in other countries compare to FDA's system, to help determine when it may be able to rely on foreign inspection and testing data as a cost-effective alternative to direct FDA inspections. In addition, the Agency has been exploring:

- ◆ Joint inspections with inspection authorities from other countries and regions.
- ◆ Using accredited third parties to conduct audits/inspections.



### Trilateral Joint Inspections

In 2009, FDA joined with EMA and Australia's Therapeutic Goods Administration to conduct a pilot program—the Active Pharmaceutical Ingredient Inspection Pilot—to demonstrate the potential for leveraging their inspection resources. Before the pilot, these agencies had been conducting separate GMP inspections at the same overseas manufacturing sites, often within just months of one another<sup>50</sup>—a needless duplication of precious resources.

Under the pilot, the three agencies planned and conducted joint inspections at participating foreign facilities, and shared information from independent inspections they had conducted over the past two to three years. These exchanges have allowed FDA to redeploy inspection resources, and alerted the Agency to sites requiring heightened scrutiny. Since then, FDA has engaged in similar projects with additional counterparts.<sup>51</sup>

### Third-Party Inspection/Audits

To enable closer regulatory cooperation, FDA and Health Canada (HC) initiated the pilot Multipurpose Audit Program in 2006. The pilot explored the potential benefits to medical device manufacturers and the agencies of using a single third party for inspections/audits to simultaneously meet FDA and HC regulatory requirements for systems quality. It was anticipated that a multipurpose audit could reduce the overall time spent on site by an official Agency audit/inspection team, reducing the regulatory burden for industry.

FDA and HC conducted 11 joint audit/inspections under the pilot, of which 10 were assessed for program benefit. Results showed that the joint approach reduced the time-in-facility spent at participating manufacturers by about one-third, on average, compared to the estimated time required for separate FDA and HC audit/inspections. In addition, FDA and HC gained a better understanding of their respective auditing/inspection approaches, providing a foundation for leveraging inspection resources in the future.<sup>52, 53, 54</sup>



The process of interaction with our regulatory counterparts around the world is proving invaluable as the United States continues to be part of the international marketplace for food, feed, and medical products.

Bernadette Dunham, Director, FDA Center for Veterinary Medicine



# RISK-BASED MONITORING AND INSPECTION

**W**ith 20 million FDA-regulated import lines entering the United States each year,<sup>55</sup> monitoring and inspection are critical to identify and prevent entry of imports that may pose risks to U.S. public health. To make optimal use of its monitoring and inspection resources, FDA is developing innovative strategies that take advantage of the latest developments in science, engineering, and information technology.



## Risk-Based Strategies to Identify Products That Pose Health Risks

The lack of rigorous, widely accepted, and globally enforced standards and approaches has at times led to dangerous public health consequences from substandard/counterfeit/falsified, adulterated, or fraudulent products. To address this risk, FDA is deploying new technologies to help the Agency detect products of concern and prevent them from ever reaching U.S. consumers. Premier among these is a sophisticated information technology system called PREDICT.

PREDICT helps FDA screen the millions of imported food and medical products that enter the United States each year to rapidly identify those that pose the greatest risk to public health. With instant access to numerous FDA and public databases, PREDICT uses data mining and pattern discovery techniques to evaluate and rank FDA-regulated imports based on their potential health risk. The system provides entry reviewers with a list of imports receiving higher risk scores, as well as those that appear to be in violation of



FDA's PREDICT model is a significant advance, institutionalizing a smart, risk-based approach to import border controls by identifying the commodities that are most vulnerable.

Margaret Hamburg, FDA Commissioner

U.S. regulations. FDA import entry reviewers use PREDICT to determine which imports should be examined or sampled for laboratory analysis; which should be referred to compliance officers for detention; and which should be cleared to enter U.S. commerce. By identifying high-risk shipments, PREDICT allows the Agency to strategically focus its resources to better protect public health.



Counterfeit drugs often look like the legitimate product, making it difficult or impossible for consumers to distinguish them.



## Rapid Product Screening for Contaminants of Concern

FDA's CDER and ORA have been collaborating to determine the feasibility of using portable analytical instruments to screen FDA-regulated products in the



Use of the portable ion mobility spectrometer to screen for active pharmaceutical ingredients in dietary supplements.

field. To be effective, such tools must be portable and easy to use, and provide rapid results with sufficient accuracy for screening purposes. FDA researchers have developed methods, now being deployed in China and India on a pilot basis, to screen for several potential contaminants in FDA-regulated products, including:

- ◆ Toxic metals.
- ◆ Diethylene glycol (a toxic but less expensive chemical substitute for glycerin) in drug syrups.
- ◆ Sibutramine, a synthetic drug used in prescription weight loss products.
- ◆ Melamine (an adulterant) in milk powder.

One such method, using an ion mobility spectrometer (IMS), has detected sibutramine—which has been linked to heart problems in some consumers—in more

than 25 percent of screened dietary supplements. All IMS results indicating the presence of sibutramine have been confirmed through laboratory analysis.



## Addressing the Challenges of Internet Commerce

The explosion of Internet commerce has led to a dramatic increase in the number of FDA-regulated products being shipped into the United States via international mail and private courier services. Many of these products are prescription drugs purchased by U.S. residents from online pharmacies abroad, a practice that, with few exceptions, is illegal.

Pharmaceuticals purchased online and shipped by mail or private courier—estimated to number more than 10 million packages per year—might not have been subjected to the safety and quality checks FDA places on products imported through proper channels, and may pose health risks to consumers. Working side by side with other federal agencies, including Customs and Border Protection and the Drug Enforcement Agency, FDA is deploying risk-based strategies at mail and private courier facilities nationwide to effectively and efficiently identify, examine, and intercept these shipments.



With large, complex supply chains, problems are rarely limited to one country, and the line between domestic and international has become almost indistinguishable.

John Taylor, Counselor to the FDA Commissioner



# GLOBAL SURVEILLANCE, PREPAREDNESS, AND EMERGENCY RESPONSE

**W**orking with partners in the United States and around the globe, FDA plays a key role in helping the United States monitor, prepare for, and when necessary respond to global public health challenges, such as international pandemics, widespread distribution of tainted products, outbreaks of food-borne illness, and infectious diseases.



## Global Surveillance

With world commerce growing larger, more complex, and even more intricately interconnected, surveillance is increasingly essential to protect the U.S. public health. FDA participates in global networks of regulators and non-governmental public health organizations, and continually monitors information from several international alert systems, including:

- ◆ **International Food Safety Authorities Network (INFOSAN).** A joint program of WHO and FAO, INFOSAN monitors international food safety events such as illnesses and outbreaks, and facilitates quick exchange of information and requests for assistance among its 177 member states.
- ◆ **European Rapid Alert System for Food and Feed (RASFF).** This system facilitates quick sharing of information when a food- or feed-related public health risk is identified by one of its European member states or organizations.
- ◆ **WHO's International Health Regulations (IHRs).** These regulations legally bind 194 States Parties to help prevent and respond to acute public health risks that can potentially cross borders and threaten people around the globe. Public health risks of

international concern include pandemics and other diseases that can spread via international travel and trade, and risks from chemical spills or leaks.

FDA also receives information on emergent public health issues through many other channels, including other U.S. and foreign counterpart agencies, industry, and the public via its call center.

## Mobile Laboratories for Emergency Response

Immediate response is imperative when it comes to food-associated outbreaks and other emergencies. FDA's mobile laboratories can be quickly deployed to areas of interest, including the U.S. borders, for rapid sample analysis. For example, FDA's microbiology mobile lab has often been used at the U.S.–Mexico border to check for pathogens on leafy greens and other fresh produce, and the Agency's chemistry mobile lab was deployed to the U.S.–Canadian border to examine food samples for pesticides and toxins.





## FDA's Emergency Operations Center

As the Agency's focal point for coordinating emergency preparedness and crisis response activities, FDA's Emergency Operations Center (EOC), operated by FDA's Office of Crisis Management (OCM), is in a constant state of readiness. In coordination with FDA Centers and Offices, OCM reviews and analyzes information about threats and hazards for early alerts to domestic and international emergencies, including disease outbreaks, natural disasters, and terrorism or other criminal acts that may require FDA action to protect U.S. public health.



FDA's Emergency Operations Center provides a central location where experts from across the Agency can convene to coordinate response to emergencies. In 2010, two separate Incident Management Groups worked simultaneously in the EOC to respond an outbreak of *Salmonella enteritidis* in eggs (foreground) and the Deepwater Horizon oil spill (background).



## Traceback Investigations

FDA uses traceback investigations to locate the source (such as a specific farm or factory) and distribution of a product implicated in a public health incident, and then takes action to prevent additional illnesses by issuing product recalls and identifying hazardous practices or violations. Tracebacks also enable the Agency to distinguish between several implicated products, and determine how the product was compromised, in order to prevent future incidents.

Due to the increasing complexity of global supply chains, tracebacks are more challenging than ever because the ingredients and finished products may come from a variety of nations and travel through several countries before reaching U.S. borders. FDA works collaboratively with international regulators to rapidly identify the sources of risk and contamination.

For example, the EOC was activated in response to the 2007 melamine crisis, when thousands of cats and dogs in the United States were sickened by contaminated pet food.<sup>56</sup> EOC worked with CVM and other FDA Offices to trace the problem back to a contaminated adulterant, melamine, that was substituted for protein in pet food ingredients shipped to the United States from China. After weeks of complex, in-depth investigative work, EOC was able to determine that the adulterated product had contaminated not only pet food, but also farm animal feed and fish feed. As soon as the full scope of the problem had been diagnosed, all contaminated products were recalled from the market and destroyed.

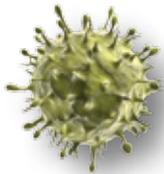


## Response to Foodborne Illness Outbreaks

FDA launched the Coordinated Outbreak Response and Evaluation (CORE) Network in August 2011 to manage surveillance, response, and post-response activities related to incidents of illness linked to FDA-regulated human and animal food. The CORE Network is comprised of a team of epidemiologists, veterinarians, microbiologists, environmental health specialists, emergency coordinators, and risk communication specialists who are charged with:

- ◆ Building on the best of how FDA currently responds to incidents of foodborne illness.
- ◆ Streamlining and strengthening the Agency's efforts to prevent, detect, investigate, respond to, and learn from incidents and outbreaks.

The team coordinates closely with FDA Offices and other U.S. agencies involved in responding to illness outbreaks. During its first few months of operation, the CORE Network directed response and post-response activities for several foodborne illness outbreaks, including a norovirus outbreak linked to frozen oyster products from Korea, and an outbreak of salmonellosis sourced back to Turkish pine nuts sold in bulk, which caused illnesses, including hospitalizations, in multiple states.



## Response to the H1N1 Influenza Pandemic

The emergence of a new influenza virus for which people have little or no immunity, and for which there is no vaccine, poses the threat of a pandemic—a global disease outbreak. CBER helps prepare the nation and the world to respond to influenza pandemics by facilitating the development, production, and regulatory review of biological products, such as vaccines. CBER also conducts post-market surveillance of these products.

On April 26, 2009, the Secretary of the U.S. Department of Health and Human Services declared a national public health emergency in response to a large number of confirmed cases of H1N1 influenza in the United States. WHO followed on June 11, 2009, with its declaration of an influenza pandemic, and FDA moved quickly to establish a command system to coordinate a response to the new pandemic and facilitate collaboration with and outreach to the Agency's U.S. and international partners. FDA established cross-cutting teams to address vaccines, antivirals, diagnostics, personal protection, and consumer protection.

CBER, which had been strengthening the U.S. influenza vaccine infrastructure and enhancing global pandemic preparedness for several years, stepped in rapidly and decisively on the research and regulatory fronts. CBER also took a leadership role in the international arena, supporting WHO's global efforts and partnering with foreign regulatory agencies to mount a coordinated emergency response. In addition, during the pandemic, WHO recognized CBER as the "Reference National Regulatory Authority" for five influenza vaccines under WHO's vaccine prequalification program, including three H1N1 monovalent influenza vaccines.

Working with the vaccine manufacturers, the Agency approved four safe and effective vaccines against the 2009 H1N1 influenza virus only three months after the WHO declaration. Two months later, FDA approved two additional vaccines, one for adults and another for children as young as six months. These approvals were achieved rapidly, while following the scientific and regulatory procedures essential to ensure the vaccine's safety and effectiveness.<sup>57</sup>



## Response to International Disasters

Natural disasters such as earthquakes, hurricanes, and floods have the potential to affect the global supply chain for FDA-regulated products, and FDA vigilance is essential to ensure that any products imported to the United States from disaster-stricken areas are safe.

The March 11, 2011, tsunami and subsequent nuclear accident in Fukushima, Japan, is a case in point. On March 22, 2011, to complement the measures taken by the Government of Japan and strengthen the global food safety net, FDA issued an import alert banning the import of all milk, milk products, fresh vegetables, and fruits produced or manufactured from Japanese prefectures near the Fukushima Daiichi nuclear reactor.

For food products from areas near the reactor but not covered by the import alert, FDA began monitoring for elevated radiation levels. FDA screened the incoming food items from Japan for the three types of radionuclides—Iodine-131, Cesium-134, and Cesium-137—that are of greatest concern to food supplies following a nuclear power plant accident, and for others as needed. As of June 1, 2011, FDA import investigators had performed over 18,000 field examinations for radionuclide contamination, and had tested almost 800 samples. Only one sample was found to contain detectable levels of Cesium, but was below levels that pose a public health concern.<sup>58</sup>

To ensure the safety of drugs from Japan, FDA established special procedures to evaluate drugs originating from the ten prefectures closest to the Fukushima Daiichi plant. FDA physically examined radiation levels of all drugs originating from these ten prefectures, and began examining and testing all injectable and inhalable drugs regardless of origin within Japan, since these drugs directly enter the bloodstream.

In response to a request from the Japanese Government for assistance designing effective risk communication, an FDA radiation expert advised Japanese counterparts about food and water safety, including the potential for radioactive contamination of current and future food supplies and the risk to consumers from ingesting contaminated food.



# ADVANCING REGULATORY SCIENCE

In today's globalized economy, FDA's engagement with global partners to advance regulatory science is essential to fulfilling its mission. Regulatory science applies basic science to develop the tools, standards, and approaches that FDA and its global counterparts use to assess the safety, effectiveness, quality, and performance of regulated products. Advancements in regulatory science can lead to more cost-effective and timely product development and evaluation; increased capacity for post-market detection of product-associated adverse events and safety assessment; and rapid resolution of incidents involving product contamination or other concerns.<sup>59</sup>

The need for strong regulatory science is urgent. Scientific advances—from sequencing the human genome to applications of nanotechnology to innovations in information technology—have the potential to transform the ability of FDA, and its international counterparts, to ensure product safety, yet development of the next generation of assessment tools has not kept pace with these advances. Harnessing advances in life sciences and engineering in the service of public health is a global endeavor, since no single country has the financial, human, or scientific resources—or answers—needed to fully ensure the safety of food, drugs, and devices. International scientific collaboration is helping FDA benefit from, and contribute to, the global regulatory community to better protect public health.



## International Leadership in DNA Microarray Research

DNA microarray technology enables regulatory and clinical scientists to simultaneously evaluate the relative expression of thousands of genes. It offers a powerful tool for understanding how genes influence individual response to pharmaceuticals or toxic substances, and for rapidly identifying early biomarkers (distinctive biological indicators) of toxicity and disease. However, standards and quality measures were needed before the technology could be applied reliably and successfully to clinical practice and regulatory decision-making.

To meet this critical need, NCTR led an international consortium in the first MicroArray Quality Control (MAQC-I) project, an unprecedented effort to develop quality control guidelines and data analysis evaluation methods for DNA microarray data. More than a hundred researchers at 51 U.S. and foreign academic, government, and commercial institutions participated. The



An NCTR scientist analyzes a readout of microarray data.



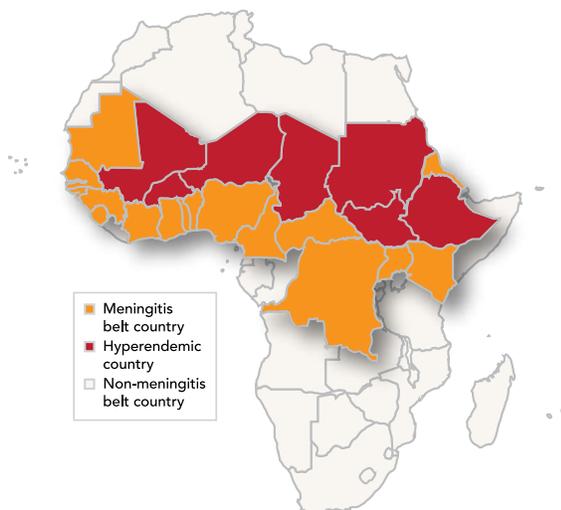
results, which were published in the journal *Nature Biotechnology* in 2006,<sup>60</sup> were a landmark in DNA microarray research and have been cited more than 1,000 times since then. *Nature Biotechnology* highlighted the MAQC-1 project in its 15th anniversary edition, published in March 2011, as it revisited ten of the most important advances and most highly cited research articles of the past five years.<sup>61</sup>

MAQC-1 provided an important foundation for deriving essential guidelines for use of microarrays in the discovery, development, and review of products regulated by FDA and its counterparts around the world. Since then, under NCTR's stewardship, the MAQC project has continued its international leadership by expanding to evaluate microarray-based predictive models (MAQC-II) and next-generation sequencing platforms (MAQC-III).<sup>62</sup>



## International Collaboration to Prevent Meningitis

The potential for infectious diseases to spread rapidly from one country to another grows ever greater as more people travel internationally and as increasing quantities of goods are shipped around the world. In response, CBER works with international partners on many fronts to reduce the risk and prevalence of infectious disease. A key example of this work is a breakthrough vaccine technology that was developed by CBER scientists and then leveraged, through an international partnership, to protect millions in Africa against meningitis.



About 430 million people, in a region called the “meningitis belt,” are at risk of meningitis in Africa.<sup>65</sup>

Deadly and debilitating, meningitis affects many thousands of people throughout Sub-Saharan Africa, killing one in ten people who contract the disease and leaving one in four survivors with permanent disabilities.<sup>63</sup> In the mid-1990s, after the deadliest meningitis outbreak in African history killed more than 20,000 people,<sup>64</sup> health ministers of several African countries turned to WHO for help. The vaccine they had been using had substantial disadvantages: it was expensive, only protected people for two to three years, and did not protect very young children or prevent infected individuals from transmitting the disease to others.

WHO convened global health leaders, including CBER, to discuss possible solutions. They agreed the most promising strategy would be to develop a potent, affordable vaccine against the group A meningitis strain, which causes 80 percent of meningitis cases in Africa. A year later, the Meningitis Vaccine Project (MVP) was established, with funding from the Bill and Melinda Gates Foundation, to develop and introduce such a vaccine.

Key to development was access to “conjugation technology,” a method that would boost the vaccine’s potency, ensure it would provide long-lasting protection, and prevent infected individuals from transmitting the disease to others. Typically, the cost for private development of such technology would render the resulting vaccines unaffordable to African countries.

CBER approached MVP to offer a solution. Through prior work over many years, CBER scientists had developed a high-efficiency, general purpose conjugation method. CBER donated this technology to the project and transferred it to MVP’s vaccine production



Photo source: M. Berlier/PATH. Used with permission.

Scientists from FDA's CBER were instrumental in developing an affordable vaccine against meningitis—the first vaccine ever developed specifically for Africa.



Mother and son with a “carte de vaccination” during the December 2010 mass vaccination campaign in Burkina Faso, Mali, and Niger against epidemic meningitis A.

partner, the Serum Institute of India (SII), at almost no cost. CBER scientists trained SII scientists at CBER facilities, and then worked with Indian scientists at SII’s research facility to help them produce the vaccine based on CBER’s conjugation technology. The method was simple and easily scalable to produce vaccines costing less than US \$0.50 per dose.

As of May 2011, nearly 20 million people had received the new vaccine. Six months after the vaccine’s introduction, the countries of Burkina Faso, Niger, and Mali reported the lowest number of meningitis A cases ever recorded. MVP hopes to vaccinate 300 million people throughout the “meningitis belt” by 2015, potentially preventing 1 million cases of the disease and saving 150,000 lives by 2020.<sup>66</sup> This effort would end meningitis epidemics in the 25 African countries of the “meningitis belt” forever.<sup>67</sup>



## Ensuring the Safe Application of Genetic Engineering Technology

First produced in the 1980s, genetically engineered (GE) animals offer a powerful approach to developing novel pharmaceutical products and many other applications that hold great promise for improving human health and welfare. Research is currently under way in the private and academic sectors on GE animals for use as food; to produce cells, tissues, and organs for transplantation; to produce high-value products such as fibers for personal protection garments; and to resist diseases such as bovine spongiform encephalopathy, to name a few.

The “rDNA construct”—the new DNA in a GE animal that confers the desired trait or characteristic—is regulated under the Federal Food, Drug and Cosmetic Act. CVM developed guidance in 2009 clarifying how the Agency regulates rDNA constructs in GE animals and what risk questions industry needs to address when seeking FDA approval.<sup>68</sup> These guidelines provided the framework for the Agency’s first approval of a GE animal—a goat that produces the human anticoagulant drug antithrombin in its milk—in 2009. They also provide a basis for ongoing dialogue with international counterparts about the safety and effectiveness of GE animals.

To develop the 2009 guidance, CVM scientists analyzed the potential risks posed by GE animals. This analysis provided the basis for development of a rigorous, risk-based approach to regulatory review that looks at potential effects of the rDNA construct on the animals themselves, on any food derived from the animals, and on the environment. CVM scientists also led the development of a critical tool for FDA’s first approval of a GE animal: a method the Agency can use to detect rDNA constructs in the approved GE animals and their edible products.

As the current world leader in the science-based regulation of GE animals, FDA is working with U.S. Government agencies to answer scientific questions to help minimize or prevent possible trade disruptions. In addition, CVM is working with its foreign counterparts to strengthen international capacity for regulatory review of GE animals.



A tool developed by FDA scientists was critical to the Agency’s approval of goats that had been genetically engineered to produce a human anticoagulant drug in their milk. The tool enables FDA to confirm the identity of these goats and their edible products.



# LOOKING AHEAD



Leaders around the world have a shared interest in and responsibility for ensuring the safety and quality of food and medical products. By working together to monitor and improve safety and quality globally, we will benefit all of the world's citizens.

Margaret Hamburg, FDA Commissioner

**T**he need for effective global engagement will only become more pronounced as the forces propelling globalization continue—or even accelerate. Over the next decade, emerging markets will continue to grow, fueling increased worldwide competition for scarce natural resources and raw materials. Facing intense market pressures to lower costs, U.S. companies manufacturing FDA-regulated products will likely move more of their operations abroad. The distinction between foreign and domestic products will continue to blur, with goods flowing through complex, multi-step supply chains that make the source of a product difficult to identify. Countries with developing economies will export greater quantities of products to the United States, leading to an anticipated dramatic rise in imports of FDA-regulated products compared to today's already high levels. Growing access to the global marketplace and increased Internet commerce will expose Americans to increasingly sophisticated threats of fraud, product adulteration, and even terrorism—threats that likely will grow as resource scarcity renders fraud and adulteration more profitable.

years from a domestic agency operating in a globalized economy to a truly global agency fully prepared for the regulatory pressures of globalization. To achieve this transformation, FDA is developing an international operating model with four core building blocks:

- ◆ **Global coalitions of regulators** dedicated to building and strengthening the product safety net around the world.
- ◆ **A global data information system and network** in which regulators worldwide can regularly and proactively share real-time information and resources across markets.
- ◆ **Expanded FDA capabilities in intelligence gathering and use**, with an increased emphasis on risk analytics and thoroughly modernized information technology capabilities.
- ◆ **Allocation of Agency resources based on risk**, leveraging the combined efforts of government, industry, and public- and private-sector third parties.



## Blazing a New Pathway

To meet the growing global challenges, FDA has committed to a fundamental shift in its approach to product safety and quality. As described in its 2011 special report, *Pathway to Global Product Safety and Quality*,<sup>69</sup> the Agency will transform itself over the next ten

To achieve a true and lasting shift in strategy, FDA will be engaging stakeholders—including global regulators, industry, academia, and other stakeholders. The Agency will also look to the U.S. Congress to help in modernizing its authorities to enable FDA to keep pace with globalization.

### Fostering Global Coalitions

Recognizing that shared concerns create shared opportunities, FDA has been working with regulatory counterparts abroad for many years to strengthen



regulatory capacity, harmonize standards, and leverage resources. However, with the increased intensity and complexity of the regulatory environment, much deeper engagement among global partners will be essential to protect public health.

FDA will work to foster and strengthen global coalitions of regulators in different product areas to build, support, and maintain a global public health safety net for consumers. FDA likely will begin by working with a core set of partners on two primary goals:

- ◆ Developing procedures to share information across borders in a more comprehensive and systematic way than is currently possible.
- ◆ Coordinating deployment of resources toward shared goals.

This work will be founded on the premise of “comparability”—that all partners will strive for comparable safety outcomes, though they may use different approaches to achieve them.

### Global Data Information Sharing

To effectively identify signals of potential future threats to public health, regulatory authorities will need rapid access to multiple sources of information around the world. FDA will work with its global partners to identify critical data for risk models and to standardize how this information is reported. This will provide the foundation for building global data and information systems and networks to facilitate regular, systematic information exchange among FDA and its partners. Such systems will enable the Agency to better identify and analyze risks globally, and apply the necessary action to prevent or minimize harm.



## Implementing a New Paradigm for Food Safety

Passage of the Food Safety Modernization Act in January 2011 provided FDA with crucial new authorities and tools to ensure the safety of imported food. These authorities create exciting opportunities for FDA to implement its Pathway to Global Product Safety and Quality in the area of food safety. For example, FSMA explicitly recognizes that food safety agencies around the world need to work together in an integrated way to achieve shared public health goals. FSMA encourages arrangements with foreign governments to leverage resources. And, FSMA directs FDA to develop a comprehensive plan to strengthen the regulatory capacity of foreign governments and their industries—for example, by training foreign regulatory agencies and food producers on U.S. food safety requirements.

Under FSMA, FDA will build a new oversight system to hold importers accountable for the safety of the food they bring into the United States. The Agency also has the power to enlist qualified third parties in certifying that foreign food facilities comply with U.S. food safety standards and to require this certification as a condition of entry for certain high-risk foods.



Working together can help us advance solutions through the development and application of new tools and approaches.

Mary Lou Valdez, FDA Associate  
Commissioner for International Programs



## WEAVING A GLOBAL SAFETY NET

Meaningful progress will depend on sustaining vigorous momentum in the United States and the global community to make these changes real and enduring. Weaving a vibrant global safety net across all borders will be challenging and require the support of many nations and organizations in light of the tough global challenges ahead. FDA is committed to productive and pragmatic dialogue and collaboration—with regulators, consumers, academics, industry leaders, and others at home and abroad—to discover and achieve new ways to promote public health in the United States and around the globe.

# ACRONYMS

AMR	anti-microbial resistance	GCP	Good Clinical Practice(s)	OCM	FDA Office of Crisis Management
APEC	Asia-Pacific Economic Cooperation	GE	genetically engineered/ genetic engineering	OCS	FDA Office of the Chief Scientist
ASEAN	Association of Southeast Asian Nations	GHTF	Global Harmonization Task Force	OF	FDA Office of Foods
AVAREF	African Vaccine Regulators Forum	GMP	Good Manufacturing Practice(s)	OIE	World Organization for Animal Health
CBER	FDA Center for Biologics Evaluation and Research	GO	FDA Office of Global Regulatory Operations and Policy	OIP	FDA Office of International Programs
CDER	FDA Center for Drug Evaluation and Research	HC	Health Canada	OMPT	FDA Office of Medical Products and Tobacco
CDRH	FDA Center for Devices and Radiological Health	HHS	U.S. Department of Health and Human Services	ORA	FDA Office of Regulatory Affairs
CFSAN	FDA Center for Food Safety and Applied Nutrition	ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use	PAHO	Pan American Health Organization
Codex	Codex Alimentarius Commission			PANDRH	Pan American Network on Drug Regulatory Harmonization
CORE	Coordinated Outbreak Response and Evaluation	IHR	International Health Regulation	PEPFAR	President's Emergency Plan for AIDS Relief
CTP	FDA Center for Tobacco Products	IMDRF	International Medical Device Regulators Forum	PIC/S	Pharmaceutical Inspection Cooperation Scheme
CVM	FDA Center for Veterinary Medicine	IMS	ion mobility spectrometer	PREDICT	Predictive Risk-Based Evaluation for Dynamic Import Compliance Targeting
EAC	East African Community	INFOSAN	International Food Safety Authorities Network	RASFF	Rapid Alert System for Food and Feed
EFSA	European Food Safety Agency	IOM	Institute of Medicine	REC	Regional Economic Community
EMA	European Medicines Agency	ISEP	International Scientist Exchange Program	SADC	South African Development Community
EOC	FDA Emergency Operations Center	JIFSAN	Joint Institute for Food Safety and Applied Nutrition	SII	Serum Institute of India
EU	European Union	MAQC	MicroArray Quality Control	SSA	Sub-Saharan Africa
FAO	United Nations Food and Agriculture Organization	MENA	Middle East/North Africa	UDI	unique device identification
FDA	U.S. Food and Drug Administration	MVP	Meningitis Vaccine Project	VICH	Veterinary Conference on International Harmonization
FSMA	Food Safety Modernization Act	NCTR	FDA National Center for Toxicological Research	WHO	World Health Organization
FY	U.S. Government fiscal year	NRA	national regulatory authority		
GCC	Gulf Cooperation Council	NZFSAN	New Zealand Food Safety Authority		

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““ As our world transforms and becomes increasingly globalized, we must come together in new, unprecedented, even unexpected, ways to build a public health safety net for consumers around the world. ””

Margaret Hamburg, FDA Commissioner



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