Ensuring Safe Foods and Medical Products Through Stronger Regulatory Systems Abroad

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Summary

Food and medical product safety is crucial for public health. The food and medical products regulatory system (hereafter, the regulatory system) is a key piece of the public health system. In the United States, the Food and Drug Administration (FDA) protects consumers from unsafe food and drugs, an ever more complicated task as increasingly food and medical products travel through complex international supply chains. The past 10 years have seen contaminated heparin and pet food reach the American market from foreign factories. Thousands of Americans die every year from food poisoning and, although much of it is home-grown, foodborne epidemics are increasingly international. This is small compared to the product safety calamities in developing countries, where fake drugs and poisoned excipients kill tens of thousands against a constant background of aflatoxin poisoning and foodborne disease.

Product safety in the United States depends on systems in faraway places. The FDA estimates that more than 80 percent of active pharmaceutical ingredients and 40 percent of finished drugs come from abroad, as does 85 percent of seafood. Congress has reacted to these trends by requiring that the FDA inspect more producers. Meeting Congress's new inspection targets will be a great effort for the FDA. More importantly, Congress's most ambitious inspection plan still monitors only a small fraction of foreign manufacturers.

The FDA cannot do its job well without substantive improvements in the capacity of its counterpart agencies in emerging economies. With this in mind, the FDA commissioned this study to identify the core elements of food, drug, medical product, and biologics regulatory systems in develop-

ing countries; to identify the main gaps in these systems; and to design a strategy the FDA and other stakeholders can use to strengthen food and medical products regulatory systems abroad.

In preparing this report, the committee heard from stakeholders from many low- and middle-income countries at conferences in Washington, DC, Beijing, São Paulo, Pretoria, and New Delhi. A brief summary of its findings and recommendations follows.

CORE ELEMENTS OF REGULATORY SYSTEMS

The committee identified the main characteristics of successful regulatory systems. First, a robust system is responsive; it can respond quickly in a crisis, and it can respond appropriately to new science and new ideas. Such a system also focuses on the outcomes and does not become overly concerned with prescribing methods that might get in the way of innovation. A robust regulatory system is a predictable system; rules are applied consistently and fairly and are designed to favor neither small nor large companies, neither imports nor domestic products. The system allocates controls proportionate to risk and regulates products with similar risks in similar ways. Finally, a robust regulatory system is independent; it is not unduly influenced by politics or money.

The main duties of a medical products regulatory authority are: product registration; the publication of clear licensure requirements; the provision of unbiased information; market entry notification; safety and effectiveness surveillance; quality control testing; inspection of manufacturers against good manufacturing practices; inspection of distributers against good distribution practices; and the evaluation of medical product performance through trials. In countries that produce vaccines, the regulatory authority is also responsible for the systematic lot release of the vaccine. The main duties of a food regulatory system are providing unbiased education and advice to all stakeholders; inspecting food production sites and processing plants against good agricultural practices and good manufacturing practices; evaluating hazard analysis and critical control points (HACCP) plans; conducting physical, chemical, and microbiological analysis of food; and doing epidemiological surveillance. These responsibilities make the regulatory system a main piece of the public health system.

Low- and middle-income country regulatory authorities are not able to execute all of these responsibilities. With this in mind, the committee identified minimal elements for a regulatory system. At a minimum, the country must have a rule-making process. This rule-making system should be open enough to allow all stakeholders to comment on new regulations. A minimally functional system also has a protocol for different agencies involved in product regulation to work together. It also has a way to identify when

regulatory action is necessary. The minimal elements of a regulatory system emphasize the processes that let the system run well. Product safety is, of course, the goal of any food and medical products regulatory system. However, at a minimum there must be a process in place that allows the system to run. When this administrative framework is in place regulators have a way to execute their product safety responsibilities.

Cooperation with counterpart regulatory agencies is a core element of a modern regulatory system. Coordination among the different regulatory agencies within a country is also necessary for product safety, including coordination at different levels of government. The use of HACCP principles to control the food system and the regulation of active pharmaceutical ingredients are examples of areas where different regulators work together to their mutual benefit.

CRITICAL ISSUES IN DEVELOPING COUNTRY FOOD AND MEDICAL PRODUCT SAFETY SYSTEMS

The committee identified nine common problems that cut across developing country product safety systems. A brief summary of these nine critical issues follows.

1. Adherence to international standards is a clear problem; it requires good infrastructure and expensive equipment. The least developed countries often lack the scientific expertise to send active advocates to international standard setting meetings. Because their representatives do not participate in any meaningful way, the countries become standard-takers, not participants in standard setting.
2. There are many related problems in controlling supply chains. Food spoils quickly without refrigeration or proper storage, and it takes too long to get to market over poor roads. The vaccine supply chain and, to a lesser extent, the medicine supply chain are prey to breaks in the cold chain and to wastage. Inventory planning and demand management are difficult in places that have neither reliable transportation infrastructure nor sufficient managerial expertise in the health workforce.
3. Problems controlling supply chains are difficult to separate from infrastructure deficits. There are serious shortcomings in the market infrastructure in low- and middle-income countries, such as lack of pest control and refrigeration. Quality-control laboratories are woefully few, and the ones that do exist have outdated equipment and often have to depend on an unreliable power supply. Local manufacturing is complicated by more basic sanitation problems. Information technology could improve the jobs of regulators

and industry in developing countries, but bandwidth is far too expensive and unreliable. All elements of the system require trained personnel, which is often scarce in developing countries.

4. A strong legal foundation is a prerequisite for food and medical product regulation. Some of the poorest countries have no laws governing product safety; others have a surfeit of confusing and contradictory ones. Enforcing product safety laws is a monumental task, one that is often neglected or executed unevenly. Product liability laws are often essentially non-existent.
5. Government regulators have too few staff, problems retaining their staff, and problems with morale. Corruption is both a cause and an effect of many of the workforce problems. Some staff are fired for political reasons; others grow frustrated and quit.
6. Regulatory responsibilities in low- and middle-income countries are often scattered among many different agencies. This is true in the United States and in many other developed countries as well, but it becomes a problem in places where the same responsibilities are assigned to different agencies or when there is no way for different agencies to communicate. Sometimes the agencies have limited authority to enforce laws; others have authority, but problems coordinating with other agencies.
7. Poor surveillance systems prevent regulators from evaluating emerging safety signals. They cannot monitor medical product safety, track epidemics, or do risk analysis without reliable surveillance data. Weaknesses in the vaccine safety surveillance system can aggravate vaccine scares. Pharmacovigilance systems are also weak; often doctors and pharmacists are not aware of their responsibilities to report adverse drug events.
8. Strong communication can do much to assuage the problems of fragmentation in a regulatory authority, but there are problems with communication among the different agencies responsible for regulation in developing countries. There are also problems communicating within agencies, especially from subordinate to senior staff. Often there is no appropriate forum for regulators to communicate with industry. Consumer groups, which communicate the public's needs to both government and industry, are often missing.
9. A push for product safety can come from the public, especially in large markets with good communications systems. When governments are accountable to their citizens, public opinion can drive political will. Politicians in emerging economies are often more concerned with economic growth. Some regulators are assigned a job that has both product promotion and regulatory responsibilities; they can do neither fully or well. Product safety is not a high

priority in countries with skeletal health systems, poor sanitation, and high mortality. Ironically, the vast increase in foreign aid for health over the past 10 years has had an unintended consequence of decreasing national governments' allocations to health, to the detriment of food and medical product safety.

STRATEGY FOR BRIDGING THESE GAPS

After analyzing the nine main gaps in food and medical product regulatory systems in developing countries, the committee developed a strategy to bridge these gaps. This strategy emphasizes public health, market incentives, risk-based investments, and international coordination.

Unsafe food and medical products are at the root of many public health problems in poor countries. Foodborne disease often causes diarrhea, which in turn aggravates malnutrition. Malnutrition compounds the many infectious diseases common in developing countries, diseases that go untreated because of an unsafe or unreliable drug supply. No one would argue that improving public health is less than essential for international development, and the regulatory system is a key piece of the public health system. Yet, donors are disinclined to invest in regulatory systems, preferring to fund disease-specific programs or improve the primary health system.

There is much room for improvement in the way donor agencies, foundations, non-governmental organizations, and multilateral organizations invest in regulatory systems, not the least of which is an emphasis on risk. It is neither good management nor good sense to divide resources equally among all regulated products. Risk assessment is the foundation of modern regulatory science. An understanding of the same should guide investments in product safety.

The market can also drive improvements to regulatory systems, but not without deliberate incentives. The American food and medical products market is strictly controlled, as are all of the most lucrative markets. In emerging economies, small- and medium-sized businesses dominate much of the pharmaceutical supply chain and vastly more of the food supply chain. Economies of scale make it difficult for these industries to adhere to the standards that would allow them to export to hard currency markets. Proper monetary incentives can help developing country producers stay competitive in the global marketplace. Similarly, stricter product liability laws can work to the advantage of producers who make safety a priority.

Product safety cannot improve without international cooperation. Universities and multilateral organizations are often adept at collaborating across borders. Regional collaboration is an efficient form of collaboration that allows less technologically advanced countries to benefit from the systems in place in neighboring countries.

INTERNATIONAL ACTION

Because of international trade, product safety failures in any one country can have ramifications around the world. The global foodborne disease outbreaks and contaminated drug scares have driven this point home over recent years. International trade is also a vehicle for economic development; jobs in high-value agriculture and manufacturing are ways out of poverty for many. Because everyone has a stake in product safety, everyone needs to take action to build regulatory systems. The committee's proposed international action will: increase investments in regulatory systems; encourage open dialogue among government, industry, and academia in emerging economies; work toward voluntary sharing of inspection results; and support surveillance.

Recommendation 5-1: In the next 3 to 5 years, international and intergovernmental organizations should invest more in strengthening the capacity of regulatory systems in developing countries. The United States should work with interested countries to add it to the G20 agenda. Investments in international food and medical product safety should be a significant and explicitly tracked priority at development banks, regional economic communities, and public health institutions. International organizations should provide assistance to achieve meaningful participation of developing country representatives at international harmonization and standardization meetings.

There is common ground where food and medical product safety, public health, trade, and economic development are mutually reinforcing. The development banks and regional economic communities work in this common ground; they should invest more in building regulatory systems in low- and middle-income countries. In particular, their investments should aim to improve the participation of scientists from these countries in international standard setting. The G20 is an excellent forum for industrialized and emerging economies to work together on development. In 2012, Mexico will host the G20 meeting. An emerging manufacturing nation with a vigorous export economy, Mexico would be an ideal leader for a global initiative on food and medical product safety. The United States and other G20 nations should support Mexico in this effort.

Recommendation 5-2: In emerging economies, national regulatory authorities, regulated industry, and industry associations should engage in open and regular dialogue to exchange expert scientific and technical information before policies are written and after they are implemented. Starting in the next 3 to 5 years, these regulatory authorities should

identify third parties, such as science academies, to convene the three pillars of a regulatory system—government, industry, and academia—in ongoing discussion to advance regulatory science, policy, and training.

A robust regulatory system depends on input from industry and academia; government simply cannot shoulder the burden alone. In some counties this will require a cultural shift. Science academies are one neutral venue that can bring stakeholders together for open dialogue; public health institutes, although usually governmental, are another. Regardless of the venue that regulatory authorities use, they need to collaborate with industry and academia when designing their policies and when reviewing them.

Recommendation 5-3: Countries with stringent regulatory agencies[1] should, within the next 18 months, convene a technical working group on sharing inspection reports with the longer-term goal of establishing a system for mutual recognition of inspection reports.

Sharing inspection reports is an important first step in mutual recognition and international regulatory harmonization. In the next 18 months countries with stringent regulatory agencies should share their inspection reports of facilities in developing countries. This is a simple step that could reduce a great deal of waste. There is no need for American and European inspectors to duplicate each other's work, especially when a vast number of facilities go uninspected. Over the next decade, these agencies should participate in a working group on mutual recognition of inspection reports. In time, regulatory authorities in emerging economies would also be able to contribute.

Recommendation 5-4: Industry associations should, over the next 3 years, define an acceptable protocol for sharing of internal inspection results among their members. After agreeing on the methods, they should regularly share their results among their members.

Sharing inspection results is sensitive but crucial to an efficient product safety system. In the next 3 to 5 years, food and medical product industry associations can work with their members to decide what information to share and how to share it. They could also encourage members to make use of modern data management and to rely less on handwritten inspection reports.

[1] Countries with stringent regulatory agencies include the United States, European Union member states, and Japan. For the purposes of this report the committee includes ICH Observers and Associates, Australia, New Zealand, Norway, Iceland, Switzerland, and Canada in the category.

Recommendation 5-5: Starting in the next 5 years, USAID, FDA, CDC, and USDA should provide (both directly and through WHO and FAO) technical support for strengthening surveillance systems in developing countries. This technical support could include development of surveillance tools, protocols for foodborne disease surveillance and post market surveillance of medical products, and training of national regulatory authority staff and national experts.

There is a wealth of surveillance expertise in the United Nations (UN) system; the U.S. government and universities have substantial technical depth in the same. These organizations need to strengthen surveillance systems in low- and middle-income countries. The CDC's PulseNet program, for example, is a surveillance program that has expanded to Latin America, Asia, the Middle East, and Europe. In the next 3 years, USAID, FDA, CDC, and USDA can work with their host country counterparts to develop manageable systems for pharmacovigilance. Within 5 years, an expansion of the CDC PulseNet program could elicit meaningful improvements in the foodborne disease surveillance systems in the poorest countries. Building a cadre of trained epidemiologists will take time, probably 10 years or longer, but is an important step of strengthening surveillance systems.

DOMESTIC ACTION

The Food Safety Modernization Act and the FDA's new *Pathway to Global Product Safety and Quality* make it clear that the agency is prepared to change its operations to keep pace with globalization. The committee recommended specific actions that the FDA and other government agencies should take to improve the capacity of regulatory authorities in low- and middle-income countries. The committee's proposed domestic action will: use risk as a guiding principle; use information technology; bridge training gaps; lead in adaptation of international standards; expand the one-up, one-back track and trace requirements; research inexpensive technology; give market incentives for supply chain management; and increase civil liability.

Recommendation 6-1: The FDA should use enterprise risk management to inform its inspection, training, regulatory cooperation, and surveillance efforts. Enterprise risk management should apply to the Agency's entire operation, and it should incorporate a number of set criteria such as country of manufacture or production, volume and type of product, facility inspection history, and trends or data shared from other regulatory authorities.

A comprehensive use of risk management should guide the FDA, and it should employ risk management for its entire operation, not merely for inspections as is often advised. In the next 3 to 5 years, the FDA should use risk to run its international programs—to choose which offices to scale up, what trainings to run, and where to run them. In the next 10 years, the agency should use risk to determine how it allocates its resources to both domestic and international programs. To this end, it may need to ask Congress to revise the law governing it.

Recommendation 6-2: The FDA should develop an information and informatics strategy that will allow it to do risk-based analysis, monitor performance metrics, and move toward paperless systems. In the next 3 to 5 years, the FDA should propose, in all its international harmonization activities, a standardized vocabulary, a minimum data set to be collected, and the frequency of data collection.

The use of an enterprise-wide risk management system depends on efficient and reliable data management and on using a data format that lends itself to appropriate international sharing. In the next 3 to 5 years, the FDA can articulate a standard data collection format and vocabulary. The FDA should work with international forums such as the World Wide Web Consortium and the Institute of Electronics and Electrical Engineers to work out a minimum key data set that it and its counterparts can collect and share. These are steps to the goal of having a paperless system in the next decade.

Recommendation 6-3: The FDA should facilitate training for regulators in developing countries. The purpose is workforce training and professional development through an ongoing, standing regulatory science and policy curriculum. In the next 3 to 5 years, the FDA should broaden the scope of FDA University to educate FDA staffers on international compliance with its regulations. In the long term, the FDA should consider the options the committee puts forth in Chapter 6.

The FDA should use its diplomatic staff abroad and its gravity at international forums to facilitate the training of foreign regulators, though not necessarily to host it. There should be a predictable, standing regulatory science and policy curriculum that regulators from abroad could work through. Training-of-trainers will also be an invaluable way to educate in all languages and reach students in remote places. Over the next 3 to 5 years, the FDA can work through existing networks, such as the Asia Pacific Economic Cooperation's Partnership Training Institute Network, to train trainers. There is also value in an apprenticeship program akin to

the CDC's Field Epidemiology Training Program. The committee understands that training regulators at an international regulatory college and developing an apprenticeship program will take about a decade. In the next 3 to 5 years, the FDA can broaden the scope of classes at its staff college to better educate American regulators on the international effects of and international compliance with U.S. regulations.

Recommendation 6-4: U.S. policy makers should integrate food and medical product safety objectives into their international economic development, trade, harmonization, and public health work. To this end, the FDA should lead in the development and adoption of international and harmonized standards for food and medical products.

The FDA is an accepted gold-standard regulatory agency; it should lead by example in the use of international standards. Harmonized standards facilitate trade and simplify compliance with product safety rules. The FDA should also work with other industrialized countries to streamline the criteria they use to evaluate conformance with standards. The FDA can also work with the U.S. Trade Representative to use international forums to promote harmonized standards for foods and medical products. In the next 3 to 5 years, the FDA can begin adopting harmonized international standards, but the full realization of integrating product safety into the larger U.S. international policy agenda will take a decade.

Recommendation 6-5: The FDA, which currently requires one-up, one-back track and trace requirements for food, should, in the next year, hold a multi-sector, international, public workshop on applying them to medicines, biologics, and (when appropriate) to devices.

Laws require food producers to identify the immediate prior and immediate subsequent recipient of all products in their supply chains. This is called one-up, one-back traceability. Expanding one-up, one-back requirements to drugs will be complicated, but all stakeholders need to think seriously about the costs and benefits of doing this. The FDA can demonstrate its commitment to strengthening global supply chains by hosting a public hearing on this topic in the next year.

Recommendation 6-6: Starting in the next 2 years, the FDA and the USDA should implement Cooperative Research and Development Agreements and other programs to encourage businesses and academia to research and develop innovations for low-cost, appropriate fraud prevention, intervention, tracking, and verification technologies along the supply chain.

The U.S. government needs to encourage research into frugal technologies that would be useful in poor countries. The USDA and FDA should pursue Cooperative Research and Development Agreements with private companies to work together in research and development; the first of these could be issued in the next 2 years. They can also collaborate directly with researchers in developing countries. The technologies developed in these collaborations would also benefit small- and medium-sized producers in the United States into the future.

Recommendation 6-7: The FDA should ensure an adequate mix of incentives to importers of food and medical products that are confirmed to meet U.S. regulatory standards. One such promising initiative is the 2-year FDA Secure Supply Chain pilot program. The FDA should evaluate this program immediately after its pilot phase (scheduled to end in 2014). The program should be expanded, if successful, to include a greater number of importers and food.

The FDA does not have the authority to regulate all the upstream activities in complex international supply chains of food and medical products. The Secure Supply Chain pilot program rewards firms that trace their products thoroughly from manufacture to entry into the United States. The results from this pilot program should be evaluated when the pilot phase is over in 2014 with the goal of expanding the project to include more importers and more products in the next 3 to 5 years.

Recommendation 6-8: Over the next 10 years, U.S. government agencies should work to strengthen the ability of those harmed by unsafe food and medical products to hold foreign producers and importers liable in civil lawsuits.

Importers carry a great deal of product liability risk when they bring products into the American market. The U.S. government should give clear guidance to producers in low- and middle-income countries on the rights of consumers and the importance of product liability laws to trade and to health. In the next decade, U.S. government agencies including, but not limited to, the U.S. Trade Representative, the Department of Treasury, and the Department of Justice should work to increase liability for unsafe food and medical products.

CONCLUSION

Over the past 30 years, international trade, outsourcing, and improvements in telecommunication have created a more unified world economic

system. This system benefits many, but it also presents new challenges. Individual countries can no longer depend on their national regulatory authorities to guarantee product safety in the domestic market. This report identifies the most pressing problems facing food and medical product regulators in developing countries. It outlines a strategy that can guide investments in regulatory capacity. It also recommends 13 specific actions the U.S. government and others could take to improve product safety and public health around the world.

The strategy for building regulatory systems and the 13 specific recommendations put forth in this report could do much to improve food and medical product safety in the United States and abroad. It was clear to the committee that product safety is a dynamic problem; it requires agile systems to respond to changing needs. The system should use enterprise risk management to inform its decisions. It is also clear that the FDA cannot act alone; it must develop ways to make the most of its extensive expertise and limited resources. Pooling data and planning inspections with other stringent regulatory agencies is an important first step. Other international organizations and regional communities are well-positioned to lead in training and education—key pieces of the solution. Finally, it has become clear that the FDA needs to refocus resources and attention on modern threats to the food and medical product supply. This will probably require rebalancing programs to give more attention to foreign producers and suppliers.