nature medicine

Outsourcing safety

With the global outsourcing of domestic drug manufacturing, the need to ensure the quality and safety of medical products has never been greater. But recent events show that the US Food and Drug Administration (FDA) is not up to the task.

The FDA has been rocked by recent scandals; for example, contaminant-laced heparin and *Salmonella*-contaminated peppers and peanut butter caused dozens of deaths last year. Similarly, in China, melamine-laced milk products were responsible for the deaths of at least six babies and the hospitalization of 300,000. These tragic events come on the heels of the distribution in Panama of cough syrup containing the poison diethylene glycol, which killed at least 100 people in 2006. Together, they underscore the urgent need to guarantee the safety of both domestic and imported food and medical products.

The issue is particularly pressing for drugs sold in the US. It is estimated that 80% of the active ingredients of prescription drugs sold in the US are now foreign made, raising the question of whether sufficient mechanisms are in place to safeguard imported pharmaceuticals. And the US is not alone in this trend to outsource drug manufacturing. In all of Europe, there remains a single factory that makes aspirin and only one that makes acetaminophen. But competing with China to produce aspirin, as with many other generics, is no longer affordable, and both factories are slated to close.

The economics of outsourcing are hard to ignore: lower wages for foreign workers reduce production costs, and companies minimize capital outlays by using existing offshore infrastructure (that is, manufacturing plants) and expertise, thereby eliminating the expense of acquiring or maintaining these resources domestically. Of course, the cost savings derived from outsourcing are dependent on a strong dollar, and, with the recent rise in value of foreign currencies such as the Indian rupee against the US dollar, the drive to outsource may be partially—although perhaps only temporarily—mitigated.

Another incentive driving outsourcing is the minimal regulatory oversight of foreign drug factories compared with that of their domestic counterparts, which reduces the cost of adhering to regulatory requirements when medicines are made abroad. The FDA is supposed to inspect US pharmaceutical plants every two years. But the frequency of inspections of foreign plants is far lower—estimated at less than once every 13 years at the current rate—and the record-keeping of such inspections seems to be lax. Follow-up inspections to ensure that problems identified at foreign factories have been corrected can take four or five years, so there is little impetus to fix issues quickly. A recent *New York Times* report indicates that of the 714 drug factories in China that export products to the US, only 15 are inspected each year. In the case of the heparin scandal, the FDA had never inspected the factory that supplied the contaminated drug.

This oversight is assumed to not be an isolated incident. According to a report submitted to the US House of Representatives by the US Government Accountability Office (GAO) in 2007, the FDA does not know how many foreign drug factories export products to the US and must be inspected. One internal database lists the number as 3,000, whereas another lists it as 6,800. The true number is unknown. The two databases are not compatible, and so errors and duplications must be identified by hand. As a result, the internal accounting is so poor that the FDA does not know which factories have been inspected, and, if they have been inspected, when, nor does it know where many of these factories are or what they make. According to the *New York Times*, some of the problems may stem from translation errors, whereas others may stem from insufficient notification to the FDA of changes in names or locations of plants. The FDA does not employ translators for its inspections abroad and instead relies on those provided by the foreign company, a clear conflict of interest. But, these excuses aside, the central issue is the archaic system inherent in the FDA, the absence of automation and the lack of modern data management. The very same issues were raised by the GAO in 1998. They have yet to be resolved.

The solution is not a return to domestic drug manufacturing. The US healthcare system is now entirely dependent on the foreign supply of drug products and does not have the manufacturing capability necessary to supply the country's needs. The process of rebuilding such capacity would take years and is not an economically viable option in today's world

of outsourcing. Instead, the process of effective—rather than cursory—oversight must be restored, and ramifications must be established for drug importers to shoulder their part of the regulatory responsibility.

In response to some of the public outcry about recent national and international food and drug scandals, the FDA established in late 2008 and early 2009 three official outposts in China, two in India and one each in Costa Rica and Brussels. Their aim is to improve the compliance of foreign exporters with US regulations for food and drug safety. Although the offices are a good initial tactic, with only eight employees described as inspectors or senior technical experts assigned to the three locations in China, and thousands of food and drug manufacturing plants to monitor, the effort may fall short of its aims.

In January, legislation was introduced to overhaul the ability of the FDA to regulate the safety of food, drugs, medical devices and cosmetics. The Food and Drug Administration Globalization Act of 2009 would require all drug and device manufacturers providing products to the US to register annually with the FDA. Fees associated with the annual registration would be used to increase the frequency of inspections at foreign plants to match that of domestic inspections. The act would require that manufacturers test for contaminants in and ensure the integrity of their raw materials, improve the transparency and security of the drug supply chain to better identify sources of contamination and increase the responsibility of importers for the safety of their products. The act also proposes to increase the monetary and criminal penalties associated with failure to comply with the legislation. It is not clear that the act will be debated this year, but, given what is at stake, it should be a priority.

The FDA is in desperate need of modernization. Its staff numbers and its funding have not kept pace with the rate of globalization of the food and drug markets and the enormous increase in US imports that require regulatory oversight. In January, nine FDA scientists sent a letter to then President-elect Obama's transition team, accusing the FDA of gross mismanagement, of catering to medical device manufacturers at the expense of safety and sound science, and of an atmosphere that discourages whistleblowers. The next FDA commissioner will inherit an agency that is failing the American public in its duty to ensure the safety of domestic and imported food, drugs and medical devices. Let's hope that the new US administration can find someone up to this daunting task.