



Trying Times at the FDA — The Challenge of Ensuring the Safety of Imported Pharmaceuticals

Stuart O. Schweitzer, Ph.D.

In recent years, the Food and Drug Administration (FDA) has faced three serious challenges to its ability to ensure the safety of the country's medical devices and drugs. The first arose when

the widely marketed drug Vioxx (rofecoxib) was shown to be dangerous enough for its manufacturer to withdraw it from the market. Previously, consumers and most physicians had assumed that the FDA's drug-approval process, though not legally guaranteeing a product's safety, could be trusted to assure the public of its relative safety. The challenge to physicians, who were forced to confront their prescribing habits, was no less than that to patients, whose assumption that an approved drug, taken as directed, would be safe was proven invalid. In response, Congress and the Institute of Medicine have called on the FDA to prioritize safety monitoring.

The second challenge recently came from the Supreme Court,

which ruled in February that FDA approval of a medical device precludes lawsuits brought by patients against the manufacturer over adverse events in state courts. Courts had previously ruled that patients harmed by a device or drug through no fault of their own could claim compensation from the manufacturer. Such cases were, admittedly, difficult, because usually the manufacturer had done nothing wrong; the courts simply took the position that the party with the deeper pockets should compensate the party with the shallower ones. The Supreme Court has changed this situation, leaving patients without recourse if the FDA has certified that a medical device is generally safe and effective. In effect, FDA approval is now a shield protecting

a manufacturer from subsequent claims — a role the agency undoubtedly never intended to play. A similar case, involving drugs, will be argued before the Court this fall.

A third challenge has now arrived from China. Baxter International has recalled its entire production of certain forms of heparin after hundreds of patients had allergic reactions and at least 19 died (the FDA has since reported a death count of 62).¹ The FDA has identified the cause of the problem as an altered form of a dietary supplement that mimics heparin when tested.² The impurity was introduced — whether intentionally or not is not yet clear — into the active ingredient at a Chinese factory before it was exported to Baxter, which manufactured the final product. This sort of problem should theoretically have been prevented by the FDA, which inspects foreign factories producing drugs and chem-

Playing “Kick the FDA” — Risk-free to Players but Hazardous to Public Health

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The Food and Drug Administration (FDA) is responsible for regulating \$1 trillion worth of consumer products, or 25% of the U.S. consumer economy — the food we eat, the cosmetics we use, the medical devices implanted in our bodies or used in our care, and the drugs we take. It is of grave concern when an agency with such pervasive effects on our lives loses the public's confidence.

Public opinion polls show that confidence in the FDA fell from 80% in the 1970s to 36% in 2006¹ — ratings usually reserved for tobacco companies and used-car dealers. Much of this deterioration in confidence can be attributed to some high-profile events, ranging from the withdrawal of Vioxx (rofecoxib) to the apparent adulteration of the heparin supply, which many observers have laid largely at the FDA's door — while ignoring the responsibilities of others and the fact that the agency's federal funding is grossly inadequate. Kicking the FDA has become a popular sport for the press and legislators, but by failing to hold others accountable, it puts the public health at serious risk while carrying no personal risk for those who play it.

How did we arrive at this crisis, and what can be done to resolve it? I submit that it is time to demand that the critics assume their own share of responsibility for the recent problems. We need to acknowledge that ensuring the safety and integrity of our food, drugs, cosmetics, and medical devices is primarily the responsibility of man-

ufacturers, with the FDA providing a regulatory framework and oversight. It is also critical that legislators recognize their responsibility to provide the agency with funding that is adequate for it to perform its important functions.

The fundamental problem is that legislators have heaped more and more responsibility on the FDA without appropriately increasing its budget. Between 1988 and 2007, additional FDA responsibilities were imposed by 137 specific statutes, 18 statutes of general applicability, and 14 executive orders.¹ At the same time, the FDA received a 2007 federal appropriation of only \$1.57 billion — less than 75% of the budget for the school district in its home county in Maryland, and about the same as the projected cost of the infamous Alaskan “bridge to nowhere.”² The number of federally appropriated personnel authorized for the FDA has decreased from 9167 in 1994 to 7856 in 2007.¹ And the remaining personnel must work with inadequate information technology: 80% of the FDA's computer servers are more than 5 years old; critical clinical trial records are stored on paper in warehouses, largely inaccessible for analysis; and the information technology budget is about 40% of that for the Centers for Disease Control and Prevention.¹

Moreover, the agency's work has become vastly more complex, thanks to new science and substantial change in the business environment. Today, industry sources its products from all over the world,

seeking the best price wherever it can be obtained. Astonishingly, an estimated 80% of the active pharmaceutical ingredients in U.S. prescription drugs are manufactured overseas, with India and China being the two largest providers.¹ Although the desire to obtain the lowest-cost supplies is understandable, this shift comes with additional responsibilities for manufacturers, who must ensure the quality, chain of custody, and integrity of their supply chain, especially by supervising the manufacturing process in countries whose regulatory environments are more lax than ours.

After a number of deaths and serious adverse reactions occurred in the United States and Germany in association with the administration of heparin, investigators discovered in March that some batches of what should have been pure heparin contained as much as 50% of oversulfated chondroitin sulfate.³ Since this substance does not occur naturally and mimics heparin in assays, it may have been introduced deliberately, as a cheaper substitute. This incident recalls a 2007 episode in which melamine introduced into pet food resulted in the deaths of a number of animals. Melamine contains a high proportion of nitrogen and was added to livestock feed from China to produce misleading results in assays for protein content, increasing the feed's value. Clearly, manufacturers need to take much stronger steps to ensure the integrity of their supply chain. Such responsibilities go far beyond

“meeting regulatory requirements.”³ Neither adulteration of drugs and food products nor the use of lead in toys can be prevented solely by regulators; prevention requires intense supervision by responsible manufacturers.

Unfortunately, the heparin incident has played out in the press and Congress as a failure of the FDA to inspect the Chinese facility, and the agency was quickly condemned for having inspected only 15 facilities in China in 2006.¹ But it is inappropriate and unrealistic to expect the FDA to ensure the integrity of every manufacturer’s entire supply chain. If a manufacturer chooses to save money by purchasing raw material from China, then it must bear the additional costs of zealous quality control and oversight in a country with a very limited regulatory system and a fluid commercial structure. U.S.

taxpayers should not have to pay to send inspectors to every factory in China to allow industry to obtain cheaper and largely unregulated products there.

It is easier to attack the FDA than to assume one’s own share of responsibility. The press, for its part, frequently reports legislators’ criticisms of the agency without providing any analysis of their voting records on FDA appropriations. But the bigger scandal is Congress’s grossly inadequate funding of the agency, which demands swift and decisive action. No longer should our legislators be able to publicly excoriate FDA employees while ignoring their own complicity. No longer should any of us berate the FDA while failing to acknowledge that we are asking it to do more and more work with fewer and fewer resources. No longer should manufacturers be

able to imply that inadequate FDA inspection is an excuse for adulteration of their product during manufacture. We must stop allowing the game of “kick the FDA” to be risk-free to participants. The public’s health is at stake, and the time for adequate federal funding of the FDA is now.

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1. FDA science and mission at risk: report of the Subcommittee on Science and Technology. Rockville, MD: Food and Drug Administration, November 2007.

2. Senators clash over “Bridge to Nowhere.” *Seattle Times*. October 21, 2005.

3. Mathews AW, Burton TM. FDA identifies contaminant in heparin batches. *Wall Street Journal*. March 20, 2008:A4.

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ical components that are intended for export to the United States. Investigations are continuing, but preliminary information shows that the FDA did not inspect the plant, though it had intended to do so. The FDA’s program for inspecting foreign drug manufacturers has been swamped by a rapid increase in overseas manufacturing of both finished drugs and chemical components.

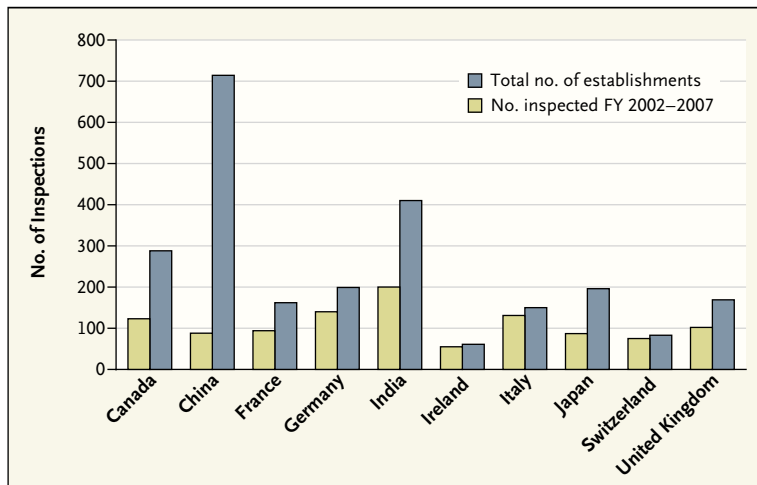
The FDA has a mandate to inspect producers of both drugs and chemicals used to manufacture drugs (active pharmaceutical ingredients, or APIs) in order to certify that plants meet the current Good Manufacturing Practice (GMP) standards. Data on the number of foreign drug and API manufacturers are difficult to obtain. The FDA uses two databases listing foreign plants that are sub-

ject to inspection. According to a 2007 report by the Government Accountability Office (GAO), one database lists approximately 3200 establishments, whereas the other lists 6800.³ Even if the smaller number is accurate, the agency inspects only approximately 7% of foreign establishments in a given year, meaning that it could take at least 13 years to inspect them all — once. The FDA cannot say how many foreign plants have never been inspected.

These inspections are conducted during the drug-development process and the preapproval stage, as well as after FDA approval. Between fiscal years 2002 and 2007, the FDA conducted 11,384 inspections,³ only 1445 (12.7%) of which were in foreign countries (see graph). The overwhelming majority of these foreign inspections

were conducted as part of a drug-preapproval process; only 179 of them were GMP inspections. Funding has also been tilted toward drug approval: total expenditures for facility inspections during this period were just over \$80 million, 39% of which was for postapproval monitoring.

According to the GAO report, the number of FDA employees who conduct GMP inspections has decreased by nearly 25% since 2002, when there were 587 such employees,³ though the number covering foreign sites increased from 100 to 141. The report also notes a number of difficulties that inspectors face at foreign sites. For instance, agency inspectors cannot conduct unannounced inspections, despite policy guidelines stipulating that inspections be conducted “without prior notification.” The agency ex-



Number of FDA Inspections of Foreign Establishments Involved in the Manufacture of Drugs for the U.S. Market, Fiscal Years (FY) 2002–2007.

The 10 countries listed are those with the most frequent inspections. The total number of establishments in each country is the number that was used by the FDA to plan its fiscal year 2007 prioritized surveillance inspections. The agency bases these counts on information obtained from previous inspections and from two databases, both of which were designed for other purposes. Data are from the Government Accountability Office.³

plains that inspectors must visit a number of facilities within a country during each overseas visit, which requires verification that the appropriate people in each plant will be available. Language barriers also hinder rigorous inspections, since inspectors must often “rely on an English-speaking representative of the foreign establishment being inspected, who may not be a translator by training.”³

Given its limited resources, the FDA has devised a “risk-based” method for prioritizing GMP inspections.⁴ It developed a model to predict which establishments are more likely to have problems maintaining GMP standards, and inspections are focused on those facilities. Although this represents a rational strategy for maximizing the effectiveness of screening within tight resource constraints, the evidence suggests that inspection needs have overwhelmed the agency’s capacity. A 2004 FDA report on the risk-based method indicated that the number of “registered human drug establishments” had

more than quadrupled during the previous 25 years, whereas the number of GMP inspections conducted dropped by more than 60%. As a result, the agency could not possibly achieve “uniformly intensive . . . inspectional coverage” for all facilities.⁴

The pharmaceutical industry is increasingly turning to overseas producers for both finished drugs and APIs. According to a report by U.S. and European fine-chemical manufacturing trade associations, the proportion of “API needs” supplied by U.S. and European Union manufacturers has declined from 90% two decades ago to less than 20% today.⁵

These production trends imply that the FDA faces a growing burden even if it merely maintains its role in testing foreign pharmaceuticals and chemicals for purity. If it must hold products to an ever-higher safety standard — given public expectations and the responsibilities implicit in court rulings — its job becomes even more daunting.

What can be done? One approach is to attempt to boost the FDA’s efficiency — an objective the agency has pursued by targeting its inspections to facilities least likely to comply with GMP standards. Hoping to increase its resources, the agency has asked Congress for large budget increases; Congress is now considering augmented funding, but neither congressional passage nor White House approval is by any means certain. Another possible source of funding is suggested by experience with the Prescription Drug User Fee Act: charging manufacturers fees to help cover the costs of the drug-approval review process increased the agency’s resources, primarily for premarket review; manufacturers could also be charged to help cover the cost of GMP reviews. Of course, no addition to the budget will be without cost. Federal funding would come at a time of severe budget restrictions and competing demands for scarce public funds, and increased user charges would push drug costs higher.

Alternatively, we could reconsider the FDA’s responsibilities. The expectation that FDA approval can guarantee drug safety is naive, since drug trials can never uncover all risks. No drug is completely safe for everyone, nor are people entitled to drugs that are entirely safe. Rather, patients and physicians are entitled to know a drug’s risks in order to weigh those risks against its expected benefits. FDA approval should not be interpreted as signaling an absence of risk. Furthermore, when a manufacturer attempts to reduce production or development costs, increased profitability must be balanced against the increased risk to consumers. Manufacturers thus have greater responsibility when production is streamlined or

component chemicals are outsourced. Ultimately, the manufacturer ought to be held accountable for any increased risk of adverse events — though the recent Supreme Court decision has made it less likely that cost-cutting actions will expose companies to financial risk.

With all these pressures coming to a head, this may be an opportune time not only to seek ways of increasing the FDA's efficiency but to consider again exactly what we expect the agency to do.

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Eliminating Blinding Trachoma

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Trachoma, a chronic bacterial keratoconjunctivitis, has always been inextricably linked with poverty. It would not even be mentioned in the curricula of many U.S. medical schools today if not for its connection with a common sexually transmitted disease: trachoma is caused by four serovars of *Chlamydia trachomatis* (A, B, Ba, and C); serovars D through K cause genital tract infection. All strains share a proclivity for epithelial surfaces. The organism is transmitted from eye to eye by hands or towels used on the face; moisture-seeking flies may play a lesser role. The genome of *C. trachomatis* has been sequenced, revealing that the trachoma strains, but not the genital-infecting strains, carry a mutation in a variable region encoding genes for tryptophan synthesis. Repeated infections of the eyes with the trachoma strains result in a sequence of tarsal conjunctivitis, scarring, shortening of the upper lid (so that the eyelashes abrade the cornea), trichiasis, and finally, corneal opacity.

Trachoma was not always so little known. It was once an ex-

clusion criterion at Ellis Island for those wishing to immigrate into the United States (see photo). The sadness caused by such exclusions was memorialized in the autobiography of New York's Mayor LaGuardia, who had worked as an interpreter at Ellis Island.¹ A "trachoma belt" was thought to exist in the United States as late as 1940.² Trachoma hospitals were established in this belt, and the last of them did not close until the 1950s (around the time that *C. trachomatis* was finally cultured), when socioeconomic improvements had resulted in steadily decreasing trachoma rates in Europe and North America.

In the developing world, by contrast, trachoma remains the leading infectious cause of blindness. The World Health Organization (WHO) reports that 55 million people remain infected, and 3 million are visually impaired or blind because of trachoma. The total at-risk population is approximately 500 million; the 2005 global distribution is shown on the world map. Although there has been a steady downward trend in trachoma

rates, the economic improvements, increased access to water, and enhanced sanitation that caused trachoma to vanish from the United States and Western Europe cannot be expected to occur in the near term in much of the developing world.

In 1997, the WHO founded its Alliance for the Global Elimination of Blinding Trachoma by the Year 2020 (GET2020), which includes ministries of health and organizations for the prevention of blindness. And in 1998, a World Health Assembly resolution called for the 55 countries where trachoma remains endemic to take steps to eliminate blinding trachoma by implementing the SAFE strategy devised by the WHO, which includes four elements proven to lead to control³: trichiasis surgery to halt corneal damage (tertiary prevention), antibiotic treatment (single-dose azithromycin, 20 mg per kilogram of body weight for children and 1 g per kilogram for adults, for secondary prevention), face washing or improved facial hygiene (primary prevention), and environmental change, including