

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.

Dr. Wood reports receiving lecture fees from the Pharmaceutical Research and Manufacturers of America, serving on the board of directors of Antigenics, and serving on the scientific advisory board of Sapphire Therapeutics, in which he holds stock options.

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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-