COMMENTARY

Under-Regulation and the Food and Drug Administration

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The Food and Drug Administration (FDA) states that its mission is "to promote and protect the public health by helping safe and effective products reach the market in a timely way, to monitor products for continued safety after they are in use, and to help the public get the accurate, science-based information needed to improve health."[1] Current concerns regarding the FDA's inability to monitor foreign imports and the inadequacy of post-approval safety requirements have called into question the ability of the FDA to remain the world's leading consumer protection agency, especially in light of recent scandals involving the cases of heparin and Avandia. This commentary will explore these issues and suggest potential solutions.

OPERATIONS ABROAD

Inadequate inspections abroad represent a key difficulty for the FDA. Whereas the agency was once well equipped to conduct inspections of drug manufacturing plants, globalization has outpaced the agency's present capabilities. According to the *New York Times* (NYT), "Eighty percent of the active pharmaceutical ingredients of drugs consumed in the United States are manufactured abroad," although less than one percent of imports are actually inspected by the FDA.[2,3] The low inspection rate is mainly due to a shortage of inspectors, a consequence of insufficient funding. Understaffing prevents overworked inspectors from adequately conducting routine inspections of manufacturing sites. In the past decade, Chinese and Indian plants have posed the largest challenges to FDA inspectors for two reasons. First, rapid growth and industrialization in those countries has generated large numbers of factories in a short period of time. Second, American and European pharmaceutical companies have outsourced significant portions of their manufacturing operations to these countries to cut costs. As a result, the U.S. currently imports 40 percent of its drugs from China and India.[2] The FDA has not been able to keep pace with this growth; the annual inspection rate of Chinese pharmaceutical plants that export drugs to the United States is on average 15 out of 714 (less than two percent).[3] The outcomes from this under-inspection have been particularly evident in recent cases involving contaminated heparin imported from China.

Heparin is an anti-coagulant derived from pig intestines that is primarily used during kidney dialysis to prevent the formation of blood clots. From November 2007 to February 2008, the FDA received thousands of reports of severe allergic reaction to the drug, which is imported primarily from China.[4] By April 2008, reports linked the contaminated heparin to at least 81 deaths in the United States alone, while 11 other countries were also affected.[5] Because the contaminant remained unidentified, FDA deputy commissioner Janet Woodcock insisted, "At this point, we do not know whether the introduction was accidental or whether it was deliberate."[4] The agency responded to the crisis by halting heparin imports, admitting "it violated its own policies by failing to inspect the China plant" where the affected drug had been manufactured.[2] The following month, the FDA acknowledged that the contamination was likely intentional because as much as one third of the substance was not blood thinner but another compound known as oversulfated condroitin sulfate; the contaminant costs only one hundredth the price of the same amount of pure heparin.[6] The plant in question was later found to fall far short of industry standards, and has since been banned from providing U.S. drug imports.

More foreign inspections are needed to ensure the safety of imported drugs. Gardiner Harris of the NYT found that although "the volume of U.S. imports has increased by more than 900 percent" since 1990, "the number of personnel financed by Congressional appropriations remained unchanged at the FDA between 1992 and 2007."[3] This demonstrates that the government has not provided the funding necessary to maintain an adequate workforce to conduct inspections abroad. An independent estimate from April 2008 suggested that the FDA would need to hire at least 500 new inspectors to equalize the inspection rate between foreign and domestic companies.[5] Moreover, representatives from both the Democratic and Republican parties have called for more FDA inspections of foreign drug plants.[7] In November 2008, the FDA opened its first overseas office in Beijing in an effort to increase its presence in China.[8] This is an important step in the right direction, but the future of the endeavor remains unclear.

THE PRESCRIPTION DRUG USER FEE ACT: A DOUBLE-EDGED SWORD

Globalization of the pharmaceutical industry has adversely affected the FDA's ability to effectively screen drugs and medical devices for approval. But safety concerns are not the only pressing priority. In the 1980s and early 1990s, demand grew for shorter approval times for pharmaceuticals to accelerate market availability. These demands culminated in the introduction of the Prescription Drug User Fee Act (PDUFA) in 1992, which requires pharmaceutical companies to pay a portion of the costs of FDA approval. The initiative was designed "to reduce drug approval times by financing the evaluation process with user fees levied on entities applying for FDA approval."[9] PDUFA has had two major consequences: drug approval times have fallen since its inception and more of these rapidly approved drugs have later been discovered to have undesired adverse effects.

Shorter drug approval time has helped pharmaceutical companies gain support from investors and facilitated rapid patient access to treatments. Indeed, PDUFA was passed in part because AIDS activists argued that the FDA was preventing patients from receiving newly developed and potentially

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life-saving drugs.[10] As a result, the duration of the review process for new drugs has been estimated to have fallen by 50 percent since the passage of PDUFA in 1992.[10] However, this effect has also decreased the incentive for drug companies to conduct large-scale safety trials after their products have been approved for market. Thus, adverse drug reaction (ADR) rates have been on the rise since the introduction of PDUFA. Mary K. Olson, an economist at Yale University, found that "a 1-month reduction in a drug's review time is associated with a 1 percent increase in expected reports of ADR hospitalizations and a 2 percent increase in expected reports of ADR deaths."[10] Her study was based on data for all new drugs approved between 1990 and 1995, the period during which PDUFA was introduced.

To achieve shorter review times, FDA approval is often granted without significant evidence that the drug performs as stated.[9] Rather, approval is frequently based on a drug's immediate effects, if they are believed to correlate with the overall intended outcome. For example, the FDA approved the drug Avandia in 1999 for the treatment of diabetes. The agency came to this decision because the drug had been shown to lower blood sugar, a so-called "surrogate endpoint" for the effect Avandia was claimed to have. [11] Eight years later, a meta-analysis of clinical studies found the drug had increased the rate of heart attacks in patients, an adverse drug reaction that could potentially have been prevented had the agency required more extensive pre-approval safety trials.[11] Alternatively, longer approval time would have deprived some patients of Avandia's real benefits.

In an interview, an FDA policy advisor stressed that although accelerated approval may be an appropriate short-term strategy to push new treatments into the market, reaching a surrogate endpoint does not ensure a quality drug.[12] Whether or not to approve a drug based on such information and when to recall a drug that has been demonstrated to cause adverse effects, the advisor noted, is an emotionally difficult decision because many patients are desperate to try any drug that might work to treat them, regardless of guaranteed safety or efficacy. Philipson and colleagues, in an analysis of drug approval policies, have similarly noted that "It is very likely that the optimal balance between speed and safety allows for the possibility that some unsafe drugs will reach the market."[9]

The FDA may soon be able to mitigate the dilemma of rapid approval and safety through a new proposal known as the Sentinel Initiative. Proposed in May 2008, this initiative would employ Medicare claims records to gather evidence of adverse drug reactions. While the current system relies on voluntary reports, the new approach is believed to be able to provide more reliable and accurate information regarding drug risks because it would entail the formation of a comprehensive database including all Medicare patients who have been prescribed a given drug.[13] However, tracking adverse events relies on data extracted from an unhealthy population, making it difficult to discriminate between pre-existing health conditions and the problems that directly result from using a drug prescribed to treat the disease.

Whether or not the Sentinel Initiative is developed into a fully functioning system, the FDA must require more post-approval double-blinded clinical safety trials to monitor adverse drug reaction rates. Continuing the regulation process past the point of market introduction would allow new drug review times to remain low, thereby granting patients access to the drugs from which they might benefit. Proper post-approval studies and the realization of an adverse drug reaction database as proposed by the Sentinel Initiative would greatly increase the safety monitoring of drugs already on the market. This combination of FDA regulation is likely to result in an optimal balance of drug availability and drug safety.

CONCLUSION

The ability for patients to receive medications without having to question their purity, safety, or effectiveness is essential to the stability of the healthcare system. However, this security is dependent on the ability of the FDA to properly regulate drug approval and importing. Presently, the agency is not able to effectively perform these duties. The FDA is unable to adequately inspect foreign drug plants; and the agency has not found the optimal balance between rapid drug approval and safety. Increased budgeting, more foreign inspection facilities, and initiatives like the Sentinel database could help to alleviate some of these issues. The challenges facing the FDA in the early 21st century are daunting and complex. Yet, it is critical that the agency receive the support and infrastructure necessary to restore consumer confidence and maintain a safe and effective healthcare system.

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