Expedited US drug approvals lack adequate post-market oversight

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Last year, the US Food and Drug Administration (FDA) approved 45 novel drugs, the highest number since the record 53 approvals in 1996. The FDA's new speedy approval process, however, has come with a loosening of regulatory oversight.

The US Government Accountability Office (GAO) issued a report in December that criticized the lack of reliable, readily accessible data on tracked safety issues and oversight for drugs approved through expedited processes by the FDA.

Expedited approvals reduce the time needed to test a drug's safety and efficacy by allowing drug sponsors to conduct shorter and smaller clinical trials, or trials that test surrogate endpoints, for drugs meant to treat life-threatening or debilitating diseases. This poses greater risks for patients, but also allows patients quicker access to drugs to treat serious diseases such as cancer or HIV/AIDS.

The reduced quantity of data on the safety and efficacy of drugs approved through expedited processes, however, makes the collection of post-approval data critical.

"The GAO report confirms my greatest fear, that FDA lacks fundamental resources and leadership in ensuring that drugs brought quickly to market are truly safe and effective," said Connecticut Democratic Congresswoman Rosa DeLauro, who requested the report, according to Bloomberg .

"If FDA is shifting more of the safety risk to consumers by allowing fewer and shorter clinical trials on expedited drugs, adequate tracking of drug safety issues and review of post-market studies are absolutely vital," she said.

For example, in 2012 the FDA approved ARIAD Pharmaceutical's cancer drug Ponatinib—which the company priced at $138,000 per year—through its accelerated approval program on the basis of promising data from phase II trials. However, larger phase III trials discovered that the drug was linked to life-threatening blood clots, which led the FDA to suspend its approval in October 2013, only allowing the drug to return to market two months later with a new "Black Box Warning" and restricted distribution system.

Similarly, Wyeth's leukemia drug Mylotarg was approved in 2000 on the basis of limited data, but removed from the market in 2010 when larger clinical trials showed that patients treated with the drug had higher mortality rates and no clinical benefits over conventional cancer therapies.

The FDA offers four types of expedited approvals: accelerated approval, priority review, fast track designation, and breakthrough designation. The GAO report focused on the latter two categories, which require drug sponsors to submit formal requests.

Drug sponsors who are granted expedited approval receive a number of benefits. For example, they are given more opportunities to meet with and get advice from the FDA, or gain access to "rolling reviews" in which the FDA reviews portions of the application as the data come in rather than waiting for the entire application. The FDA can also reduce the approval time by requiring shorter, smaller and fewer clinical trials—even eliminating phase three clinical trials.

The FDA may also allow the drug sponsor to employ surrogate or intermediate clinical endpoints—measures that are reasonably likely to predict clinical endpoints, such as survival. For example, a clinical trial testing a cancer drug might allow the drug sponsor to use the surrogate endpoint of tumor shrinkage, which may reasonably predict the clinical endpoint of patient morbidity or mortality.

Between October 1, 2006 and December 31, 2014, the FDA received 772 requests for fast track designation, about two-thirds (525) of which were granted; since July 2012, when the breakthrough designation was first established, the FDA received 225 breakthrough designation requests with about one third (71) granted. Oncology and antiviral drugs were the most common product categories. Overall, about one quarter of all drugs approved between 2006 and 2014 used at least one of the four expedited programs.

The FDA continues to monitor a drug's safety after approval through its internal database known as the Document Archiving, Reporting, and Regulatory Tracking System (DARRTS). Furthermore, the FDA can request or require (as a condition of approval) post-market studies or confirmatory trials. If a drug sponsor fails to do so, or if the

post-market studies do not confirm the drug's safety and efficacy, the FDA has the authority to change the drug's label or even withdraw the drug from the market.

The GAO report, however, shows that the FDA is not fulfilling its post-market oversight obligations. The GAO found that the "majority of potential safety issues" identified were not being tracked by DARRTS. Of the 1,400 post-market studies submitted between March 2008 and September 2013, over half were delayed or overdue. There were data reliability problems with DARRTS and the data was not readily accessible to FDA staff.

These problems were attributed to understaffing—the FDA's Center for Drug Evaluation Research is approximately 10 percent below its authorized staff ceiling—and competing priorities, such as meeting the timelines for reviewing drug applications established by the 1992 Prescription Drug User Fee Act.

Although the FDA plans to revise and streamline the process for reviewing and tracking safety issues, the GAO report states that the agency does not have comprehensive plans to address the problems.

This is an ongoing issue. A 2006 study by the Department of Health and Human Services' Office of Inspector General found that the FDA could not readily identify the progress of post-market studies. In 2008, the FDA hired a contractor to help meet the requirements of the 2007 FDA Amendments Act who discovered a backlog of more than 500 post-market studies not yet reviewed by the FDA. And, in 2009, a GAO report found that the FDA did not routinely monitor the status of post-market studies.

Concerns over patients getting access to potentially lifesaving drugs led to the first compassionate-use programs in the 1960s, while pressures to obtain early access to investigative drugs intensified in the 1980s with the emergence of the AIDS crisis. The FDA created a fast-track component (Subpart E) to its rules for approving drugs treating serious or life-threatening conditions in 1988 that, for example, eliminated the need for phase three trials. In 1992, the agency initiated an accelerated-approval pathway (Subpart H) that allowed the use of surrogate endpoints instead of clinical endpoints.

In 1992, Congress enacted the Prescription Drug User Fee Act (PDUFA) whereby the FDA would collect "user fees" from drug companies, allowing the FDA to hire more scientists. The legislation also set formal deadlines (6 months for priority applications, 12 months for standard ones) for approval decisions. It was not until 2007 that user fees could be allocated to cover post-approval, drug-safety activities.

The PDUFA resulted in a spike in drug approvals in the mid-1990s (thus, the record 53 approvals in 1996) as a backlog of drug applications were filed. By the 2000s, drug approval times in the US were quicker than in Canada in Europe. "However, early access and shortened development and review times have also been associated with negative public health outcomes," notes a 2014 article published in the *New England Journal of Medicine.*

"Such findings are predictable because of the more limited data on which expedited drug approvals are based. Although neither the fast-track nor the accelerated-approval pathways changed the legal standards for approval—which is still effectiveness with acceptable risk—they reduced the quantity of evidence needed to meet this standard and altered the nature of that evidence," says the article.

Starting in the 1970s, the FDA began to condition some drug approvals on the subsequent completion of post-approval studies. While around 30 percent of drugs were approved in the 1980s with this requirement, this figure had increased to approximately 80 percent by the early 2000s.

In 2012, Congress created a new breakthrough-therapy designation that allowed for even looser surrogate endpoints to be used in clinical trials, as part of the FDA Safety and Innovation Act. "The breakthrough-therapy designation continued the trend of applying increasingly flexible evidentiary standards to determine the qualification for expedited development and approval programs," says the NEJM article.

The reduction in drug approval time is only partly driven by patient demand. Pharmaceutical companies have a vested interest in reducing approval times because it gives them a longer period of market exclusivity before their drug patent expires—even if this means greater health risks for patients.