Caution urged over the FDA's new breakthrough designation

With the establishment of the 'breakthrough therapy' designation in July 2012, the US Food and Drug Administration (FDA) now offers four expedited review and approval pathways intended to rapidly bring drugs for serious diseases into the hands of patients who need them. No breakthrough-designated drugs have yet been approved. But with more than two dozen therapies granted the designation since applications started to roll in a year ago, some researchers are now raising concerns over whether patient safety is being overlooked in the pursuit of speeding drugs to market.

"The breakthrough drugs pathway provides yet another even faster pathway to allow approval of drugs on the basis of very limited data," Aaron Kesselheim, who studies pharmacoeconomics at the Brigham and Women's Hospital in Boston, told *Nature Medicine*. "Drugs need to be approved efficiently and rigorously—and I don't think that second half of that equation is being emphasized."

Kesselheim spoke on the implications and consequences of the breakthrough designation at a congressional briefing in Washington, DC, on 4 September. The event was sponsored by the Patient, Consumer and Public Health Coalition, an informal healthcare advocacy group, and also featured Diana Zuckerman, president of the Cancer Prevention and Treatment Fund, a Washington, DC–based nonprofit.

A primary concern raised at the briefing was that drugs evaluated under expedited review mechanisms are often approved off the back of surrogate endpoints, which are easier and quicker to collect than clinical endpoints. These outcome measures, which commonly involve laboratory tests for particular biomarkers, are thought to be tightly linked with ultimate therapeutic benefit, such as patient improvement or survival. But even though that supposition has been confirmed in some areas of medicine, such as in cardiology, where cholesterol levels are usually an accurate predictor of heart disease, surrogate endpoints remain controversial, as they don't always capture the true outcomes of interest.

FDA giveth, FDA taketh away

As a contingency of surrogate endpoint–based approval, the FDA requires drug sponsors to run what are known as phase 4 confirmatory trials. In principle, these post-marketing surveillance studies can be used to reverse approval decisions if they don't confirm clinical efficacy and safety. However, such trials are not always executed with the same scientific rigor as earlier-phase investigations, according to Kesselheim. And even when they are and the findings suggest revoking an approval, attempts to remove drugs from the market are often met with fierce opposition from drug companies, patients and doctors alike—as was the case with the breast cancer drug Avastin (bevacizumab; see *Nat. Med.* **17**, 233, 2011).

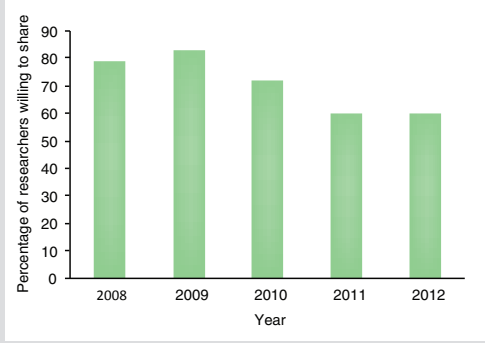
"There needs to be attention paid to how these breakthrough drugs are going to be used when they are approved and to ensure that the post-approval studies are done on a timely and rigorous basis," Kesselheim says. "If they turn out to show that the drugs don't actually work, then the designations and approvals must be withdrawn."

Despite the criticisms lobbed at the breakthrough designation, the FDA's commitment to accelerating the approval process seems to have more supporters than detractors—and, in fact, many enthusiasts continue to seek ways to make the process faster still. On 6 September, for example, Friends of Cancer Research (FOCR), a Washington, DC–based think tank, convened a local meeting to discuss strategies to further facilitate breakthrough therapies that rely on a companion diagnostic device. Earlier this year, the FDA also held a public hearing to discuss the possibility of creating yet another approval pathway for drugs intended to address unmet medical need.

"We've created pathways to keep up with the science," says Margaret Anderson, executive director of the Washington, DC–based advocacy organization FasterCures, who attended the FOCR meeting. "I think the agency is well aware that there is a crushing need for more treatments."

Kevin Jiang

Scientists express growing reluctance to share study protocols



Scientific papers include an abundance of information about methods and results. But sometimes more background details are sought by interested parties in order to precisely replicate the experiment described. However, authors seem less willing to share these additional details about their study protocols than they have been in the past, according to a survey of 389 authors who published studies in the *Annals of Internal Medicine*. The findings, presented on 9 September at the International Congress on Peer Review and Biomedical Publication in Chicago, found that over the five years studied the percentage saying they would be willing to do so has dropped from almost 80% to only 60%.

A lack of incentives for sharing might be partly to blame. "There's no recognition, no promotion and no profit for scientists who share more information," says Steven Goodman, a clinical research expert at Stanford University School of Medicine in California, who was part of the team that evaluated the survey results.

The challenge of accessing extra information not detailed in research papers is further exacerbated by time, according to a study presented at the peer review congress in Chicago by Timothy Vines, a managing editor of *Molecular Ecology*, based in Vancouver, Canada. Vines and his colleagues tried to contact the authors of 516 papers published between 1991 and 2011 that used what is known as a discriminant function analysis (DFA) on morphological data from a range of organisms. The likelihood of a successful background data request declined by 7% a year going backwards in time, as many of the authors reported that the information was lost or on inaccessible hardware. Vines says that the results of his study should spur action: "This is exactly why journals need to enact and enforce mandatory data-archiving policies."

Elizabeth Devitt