


The Declining Standards of FDA Drug Approvals

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By [Maryanne Demasi](#) August 20, 2022 August 20, 2022 [Policy](#) 5 minute read

The US Food and Drug Administration (FDA) has a legal obligation to protect the public and ensure that the benefits of medicines outweigh the harms before being marketed to people.

But the agency's increasing reliance on pharmaceutical industry money has seen the FDA's evidentiary standards for drug approvals significantly decline.

The need for speed

Since the enactment of the 1992 Prescription Drug User Fee Act (PDUFA), the FDA's operations are kept afloat largely by industry fees which have increased over 30-fold from around \$29m in 1993 to \$884m in 2016.

Industry fees were meant to speed up drug approvals – and they did. In 1988, only 4% of new drugs introduced onto the global market were approved first by the FDA, but that rose to 66% by 1998 after its funding structure changed.

Now, there are four pathways within the FDA which are designed to speed up drug approvals: *Fast Track*, *Priority Review*, *Accelerated Approval*, and *Breakthrough Therapy designation*.

As a result, the majority (68%) of all new drugs are approved by the FDA via these expedited pathways.

While it has improved the availability of transformative drugs to patients who benefit from early access, the lower evidentiary standards for faster approvals have undoubtedly led to harm.

A study focusing on drug safety found that following the introduction of PDUFA fees (1993-2004) there was a dramatic increase in drug withdrawals due to safety concerns in the US, compared to the period before PDUFA funding (1971-1992).

The researchers blamed changes in the “regulatory culture” at the FDA which had adopted more “permissive interpretations” of safety signals. Put simply, the FDA’s standards for approving certain medicines became less stringent.

Consequently, faster approvals have resulted in new drugs that are more likely to be withdrawn for safety reasons, more likely to carry a subsequent black-box warning, and more likely to have one or more dosages voluntarily discontinued by the manufacturer.

Evidence – Lowering the Bar

For accelerated drug approvals, the FDA accepts the use of surrogate outcomes (like a lab test) as a substitute for clinical outcomes.

For example, the FDA recently authorised the use of mRNA vaccines in infants based on neutralising antibody levels (a surrogate outcome), rather than meaningful clinical benefits such as preventing serious covid or hospitalisation.

Also last year, the FDA approved an Alzheimer’s drug (aducanumab) based on lower β -amyloid protein levels (again, a surrogate outcome) rather than any clinical improvement for patients. One FDA advisory member who resigned over the controversy said it was the “worst drug approval decision in recent US history.”

This lower standard of proof is becoming increasingly common. An analysis in *JAMA* found that 44% of drugs approved between 2005-2012 were supported by (inferior) surrogate outcomes, but that rose to 60% between 2015-2017.

It is a huge advantage to the drug industry because drug approvals may be based on fewer, smaller and less rigorous clinical trials.

– Pivotal trials

Traditionally, the FDA has required at least two ‘pivotal trials’ for drug approval, which are typically phase III clinical trials with ~30,000 subjects intended to confirm the drug’s safety and efficacy.

But a recent study found the number of drug approvals supported by two or more pivotal trials fell from 81% in 1995-1997 down to 53% by 2015-2017.

Other important design aspects of pivotal trials, such as “double blinding” fell from 80% in 1995-1997 down to 68% by 2015-2017 and “randomisation” fell from 94% to 82% in that period.

Similarly, another study found that of the 49 novel therapeutics approved in 2020, more than half (57%) were on the basis of a single pivotal trial, 24% did not have a randomisation component, and almost 40% were not double-blinded.

– *Post-authorisation studies*

Following an accelerated approval, the FDA allows drugs onto the market before efficacy has been proven.

A condition of the accelerated approval is that manufacturers must agree to conduct “post authorisation” studies (or phase IV confirmatory trials) to confirm the anticipated benefits of the drug. If it turns out that there is no benefit, the drug’s approval can be cancelled.

Unfortunately though, many confirmatory trials are never run, or they take years to complete and some fail to confirm the drug is beneficial.

In response, the FDA rarely imposes sanctions on companies for failing to adhere to the rules, drugs are rarely withdrawn and when penalties are applied, they are minimal.

An embattled agency

The FDA thinks its main problem is ‘public messaging’ so the agency is reportedly seeking a media-savvy public health expert to better articulate its messaging going forward. But the FDA’s problems run deeper than that.

A recent Government Accountability Office report revealed FDA staff (and other federal health agencies) did not report possible political interference in their work due to fear of retaliation and uncertainty about how to report such incidents.

Over the course of the pandemic, employees “felt that the potential political interference they observed resulted in the alteration or suppression of scientific findings...[and] may have resulted in the politically motivated alteration of public health guidance or delayed publication of covid-19-related scientific findings.”

Political interference has compounded an already problematic interference by the drug industry. The policy changes enacted since the 1992 PDUFA fees, have slowly corrupted the drug regulator, and many are concerned its decisions about drug approvals have prioritised corporate interests over public health.

Independent experts now say the declining evidentiary standards, shortening approval times, and increasing industry involvement in FDA decision-making, has led to distrust, not only of the agency, but in the safety and effectiveness of medicines, in general.

Originally appeared on the author's [Substack](#)

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