



## Evolving nature of evidence required by FDA to approve new drugs

This brief, based on systematic reviews conducted in collaboration with the Program on Regulation, Therapeutics, And Law (PORTAL), provides background on the evidence required by the Food and Drug Administration (FDA) to support drug approval. It highlights changes in the amount and extent of preapproval effectiveness and safety testing as well as the quality and timeliness of required post-market studies. It then offers a variety of policy options.

For definitions of terms used in this brief, please see the Glossary on page 3.

### Main takeaways:

- New drugs are being approved based on fewer and shorter trials, and often based on surrogate measures rather than actual clinical benefit.
- This trend increases the importance of evidence collection after approval and clear disclosure to patients about what is known about drug safety and effectiveness.
- Postapproval studies are often delayed or may not be completed at all.
- Improving access to essential evidence on drug safety and effectiveness can be achieved through a number of policy options.

### Background

In the U.S., the FDA is responsible for approving new drugs once they have been determined to provide benefits that outweigh known and potential risks. Manufacturers must submit to the FDA substantial evidence of their drugs' effectiveness as well as sufficient evidence of safety based on adequate and well-controlled trials. Characteristics of high-quality trials include appropriate comparators, randomization, blinding, use of meaningful clinical endpoints (measures of how patients feel, function, or survive) or validated surrogate measures, and sample sizes large enough to power statistical analyses.



The FDA has historically preferred new drugs to be supported by 2 adequate and well-controlled trials because any 1 trial could be subject to undetected systematic biases, although the law permits approval based on 1 pivotal trial with other supporting evidence. The agency retains broad discretion on the extent of clinical testing needed for approval and exercises this flexibility frequently for new drug approvals.

Because preapproval testing inevitably leaves some remaining questions about a new drug's effectiveness or safety, manufacturers are often obligated by the FDA to collect further evidence to clarify important unresolved questions after approval. These come in 2 varieties:

- Postmarket requirements (PMRs) are studies that manufacturers are required by law to conduct after a drug's approval.
- Postmarket commitments (PMCs) are studies that the manufacturer and FDA agree to conduct as a condition of approval.

### Issues

In recent years, research has documented changes in the amount and extent of effectiveness and safety testing before drug approval. Studies have also raised concerns about the quality and timeliness of PMRs and PMCs.



## Premarket evidence trends:

To reduce the time and cost of drug development, the FDA is now approving new drugs based on fewer and smaller clinical trials. Trials supporting new drug approvals also frequently exclude or underrepresent certain populations (i.e., the elderly, children, people of color) for whom benefits and risks need to be identified postapproval.

Comparing drugs approved in 1995 through 1997 to 2015 through 2017:

- The number of drug approvals supported by 2 or more pivotal trials decreased from 81% to 53%.
- Use of double-blinding decreased from 80% to 68%.
- Randomization decreased from 94% to 82%.
- Use of active comparators decreased from 44% to 29%.

Among the 84 pivotal trials supporting 53 new drug approvals in 2020:

- Slightly over half were double-blinded.
- Two-thirds were partially or completely randomized.
- 40% relied on a historical control, which can be problematic because the context of treatment for the historical sample might be different.

Another trend in pivotal trials has been an increased reliance on surrogate measures as trial endpoints instead of direct patient-benefit outcomes. For example, in clinical trials for cancer drugs, reduction in tumor size may be used as a surrogate measure instead of direct measurement of overall survival rate. Research has shown that surrogate measures may not always accurately predict the actual clinical

benefit of a drug. Still, the FDA has increasingly accepted surrogate measures: 44% of drugs approved in 2005 through 2012 were supported by surrogate measures compared with nearly 60% of drugs approved in 2015 through 2017.

The characteristics of pivotal trials have changed for a number of reasons. It may be impractical to enroll large numbers of trial subjects when testing drugs for certain rare diseases or conditions. In addition, about three-quarters of new drugs in recent years have qualified for expedited regulatory pathways that permit approval based on more limited evidence (i.e., Accelerated Approval, Priority Review, Breakthrough Therapy, Fast Track).



## Postmarket evidence trends:

With less extensive preapproval testing, the importance of evidence collection increases in the postapproval period. PMRs and PMCs generate more knowledge

about a new drug's effectiveness and safety, but manufacturers' completion of expected postapproval studies is of uneven quality and timeliness. Delayed evidence means prescribers and payers may be obligated to make clinical or reimbursement decisions without key information.

In a recent review of the amount, type, and timeliness of PMCs and PMRs attached to new drugs at the time of approval, we found:

- Among the 474 reportable PMRs and PMCs attached to drugs approved from 2013 to 2016, 70% were completed or expected to be completed by the end of 2020.
- Of those studies completed or expected to be completed by 2020, approximately three-quarters were late.
- Studies that were completed late (190 PMR and PMCs) were late by a median of two-quarters.

Despite having statutory authority to do so, FDA has not imposed any civil monetary penalties when postmarketing studies are delayed or not completed. Delayed PMRs and PMCs lead to unnecessary spending on drugs with uncertain benefits and unknown safety risks and may impact the quality of patient care.

## Policy Options

### Policy reform should increase the quality of efficacy and safety data. Options include:

1. Promote generation of high-quality preapproval evidence by clearly stating the reasons for particular study designs, pivotal trial endpoints, and patient populations.
2. Develop explicit criteria for use of surrogate measures and ensure transparency in the decision to allow their use. The FDA should create a publicly available record of clinical endpoints by indication with outcomes that are commonly used as surrogates for those endpoints and the evidence base underlying each of those surrogates.
3. Streamline the thicket of expedited designations to reduce administrative burdens on the FDA.
4. Provide FDA with greater authority to ensure completion of required postmarket trials, which could include automatic institution of civil monetary penalties when they are not met or greater clarity in the labeling related to outstanding PMRs or PMCs.
5. Require sponsors to study clinical endpoints in postapproval trials when a drug is approved using a surrogate as the primary endpoint and minimize delays in gathering postapproval evidence by ensuring postmarket studies are conducted under reasonable time requirements.
6. Ensure that key information about a drug's safety and efficacy at the time of approval is communicated appropriately to patients and providers, and that updates about postapproval evidence are effectively disseminated.

## References

This document summarizes the research conducted by the Program on Regulation, Therapeutics, and Law (PORTAL), Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, in collaboration with Kaiser Permanente. Full citations for this document can be found at: [kpihp.org/references-ics](https://kpihp.org/references-ics).

## Glossary

- **Comparators:** An active control or a placebo used in a clinical trial to study the effect of a treatment.
- **Randomization:** A strategy to reduce bias in trials. Assigning trial subjects to an investigational treatment or control group using an element of chance.
- **Blinding:** A strategy to reduce bias in trials. In a single-blind trial, patients do not know if they are receiving the experimental treatment or the comparator. In a double-blind trial, neither the patients nor the researchers know which patients receive the experimental treatment or the comparator.
- **Meaningful clinical endpoints:** Endpoints that measure how patients feel, function, or survive.
- **Validated surrogate measures:** A clinical trial endpoint used as a substitute for a direct measure of how a patient feels, functions, or survives. If validated, the surrogate is one in which the treatment effect on the surrogate corresponds to the effect on the intended clinical outcome.
- **Sample size:** The number of trial subjects in a study.
- **Pivotal trial:** A pivotal trial is, or could be, the basis or FDA approval.

