

FDA Announces a Single Pivotal Trial as the New Default Standard for All Drug Approvals and Unveils a Plausible Mechanism Framework for Individualized Therapies

WRITTEN BY

Kyle A. Dolinsky | Samarth Parikh

On February 18, 2026, U.S. Food and Drug Administration (FDA) Commissioner Martin Makary and the outgoing director of the Center for Biologics Evaluation and Research (CBER) Vinay Prasad published an article in *The New England Journal of Medicine*,^[1] in which they announced FDA's new default position to require only a single pivotal trial for all drug approvals instead of the current default standard requiring two trials. A few days later, on February 23, 2026, FDA marked Rare Disease Week by releasing a draft guidance titled "Considerations for the Use of the Plausible Mechanism Framework to Develop Individualized Therapies that Target Specific Genetic Conditions with Known Biological Cause" (the Plausible Mechanism Guidance).^[2] The Plausible Mechanism Guidance showcases FDA's commitment to expedite the development process of rare disease drugs. In this guidance, FDA formalizes a new framework for generating sufficient safety and efficacy data to support approval of individualized treatments — particularly genome-editing and RNA-based therapies.

This article provides an overview of these intertwined developments and discusses how FDA's policy positions can benefit drug sponsors by bringing their drug treatments to market faster, key considerations for drug sponsors during drug development, and next steps for drug sponsors as the new policy goes into effect.

Key takeaways:

- Sponsors should discuss early with FDA whether a single trial will be acceptable for their drug approval, as FDA has reserved the right to demand more than one trial.
- Approval standards remain unchanged — sponsors must still provide "substantial evidence" of effectiveness and should carefully design their single trial accordingly.
- It is unclear whether FDA will put greater emphasis on confirmatory evidence.
- The timing of FDA's policy, along with the agency's post-market initiative to collect robust data, suggests that sponsors could have greater post-marketing obligations. This may be especially true for drugs covered by the Plausible Mechanism Guidance, for which there may be limited safety data at the time of approval.
- Plan early to identify sources, biomarkers, clinical outcomes, and observational protocols for the collection of safety and efficacy data in trials that will likely have a limited number of participants.
- For drugs covered by the Plausible Mechanism Guidance, Chemistry, Manufacturing, and Controls (CMC) development must evolve concurrently with clinical development.

Single Pivotal Trial as the New Default Standard for all Drug Approvals

Makary and Prasad published a new article in *The New England Journal of Medicine*, announcing a new FDA default standard requiring only one adequate and well-controlled study, combined with confirmatory evidence, for novel drug product approvals instead of the older default standard, which required two trials. The new standard is not entirely out of the blue: since 1997, FDA has had statutory discretion to approve drugs based on one adequate and well-controlled study instead of two; new drugs in oncology and rare diseases have often been approved based on a single trial; the accelerated approval pathway similarly requires one trial for initial approval; since 2020, most new molecular entity approvals have relied on a single pivotal trial; and in 2024 that proportion peaked at 66%.^[3] The difference is that FDA is eliminating the two-trial “dogma” that it believes “anchor[s] individuals and institutions psychologically” in a manner that has hindered innovation. By defaulting to one clinical trial, FDA expects to spur innovation, “reduce costs for sponsors and will speed drugs to market.”

In abandoning the two-trial standard, the authors criticize the historical reliance on two clinical trials and state that modern developments provide better methods to obtain credible causal evidence. Although FDA originally implemented the two-trial standard to protect against the likelihood of obtaining a false positive result, a better understanding of mechanisms of action and other biological inferences can provide alternative credible evidence of effectiveness.

Notably, the authors maintain that FDA has not relaxed its standard for drug approvals, which means that drug sponsors will still need to provide “substantial evidence” of effectiveness as required under Section 505(d) of the Food, Drug, and Cosmetic Act (FDCA) and its corresponding regulations. FDA even believes changing the default from two trials to one may increase regulatory scrutiny because greater attention will be placed on the one trial. That claim seems speculative at best, but drug sponsors should still ensure that their one clinical trial is robustly designed and should consult with FDA from the outset if they hope to rely on the single trial.

Finally, the authors explain that two trials may still be necessary in exceptional cases, including “if an intervention has a nebulous, pluripotent, or nonspecific mechanism of action; if it affects a labile, short-term, or surrogate outcome; or if a trial has some underlying limitation or deficiency.” The authors clarify that FDA reserves the right to demand additional studies based on FDA’s examination of all aspects of study design with particular focus on controls, end points, effect size, and statistical protocols.

Plausible Mechanism Guidance

The Plausible Mechanism Guidance identifies alternative ways in which sponsors can generate substantial evidence of effectiveness in certain rare diseases where it may not be feasible to conduct large scale clinical trials. Specifically, it applies only to diseases with a well-characterized, identifiable molecular or cellular abnormality, and to therapeutic products that target the underlying abnormality, its proximal pathogenic pathway, or a well-characterized downstream or compensatory mechanism with a clear mechanistic rationale. The product must target the abnormality relying on a well-characterized natural history of the disease. The product must successfully drug the target, edit it, or both, and the sponsor must demonstrate improvement in clinical outcomes or course of disease. Although the guidance focuses on genome editing and RNA-based therapies, its framework applies to other types of individualized therapies “that target a specific pathophysiologic abnormality serving as the root cause of a disease.”

The guidance does not establish a new regulatory pathway or change FDA’s current marketing approval standard requiring “substantial evidence” of effectiveness. Rather, it addresses the evidence required to obtain approval via existing pathways. For the diseases and therapies covered by the guidance, substantial evidence of effectiveness is informed by factors such as clinical context for the disease, the level of unmet medical need, and the challenges involved in enrolling patients in a clinical trial. Consistent with FDA’s new default policy, substantial evidence can be established with a single adequate and well-controlled trial with confirmatory evidence. Because clinical investigations in this context will include a small sample size, investigation results must be robust to exclude any chance findings. Confirmatory evidence can be generated from clinical or non-clinical data and may include mechanistic or pharmacodynamic data, confirmation of target engagement, exposure-response on biomarkers and clinical outcomes, among others.

In addition to requiring only a single trial, FDA may offer additional flexibility for trial design and loosen other criteria to generate substantial evidence of effectiveness. For example, “in patients for whom the natural history of the disease in the untreated state can be reasonably characterized, it may be possible for an externally controlled clinical investigation that assesses a patient’s change following treatment compared to baseline to serve as the adequate and well-controlled clinical investigation necessary to support approval/licensure.”

Next Steps

Although Makary and Prasad have announced a new FDA default standard requiring only one adequate and well-controlled study, supplemented by confirmatory evidence, for all novel drug product approvals, FDA has issued the policy without any accompanying guidance document. Accordingly, sponsors should exercise caution before modifying their clinical programs in response to this change, as future developments not reflected in *The New England Journal of Medicine* article may further clarify or alter FDA’s expectations. While awaiting additional guidance, it is prudent for sponsors to engage early with FDA to discuss trial design, endpoints, comparators, and other key trial elements before implementing any program changes.

For individualized therapies, the additional flexibility FDA is offering under the plausible mechanism framework can allow sponsors to expedite their drug development process. Notably, the Plausible Mechanism Guidance is a draft guidance, and FDA is accepting comments from sponsors and other interested parties until April 27, 2026. Even though the guidance is not finalized, FDA has likely initiated changes within the agency in line with the draft guidance’s recommendations. This means that sponsors should engage early with FDA to discuss whether their clinical program qualifies for the plausible mechanism framework and to identify sources of efficacy and safety data, types of confirmatory evidence, post-marketing commitments, and other considerations.

[1] Prasad, V; Makary, M, [One Pivotal Trial, the New Default Option for FDA Approval — Ending the Two-Trial Dogma](#), 394 N. Engl. J. Med. 815 (2026).

[2] U.S. Food & Drug Admin., [Guidance for Industry: Considerations for the use of the Plausible Mechanism Framework to Develop Individualized Therapies that Target Specific Genetic Conditions with Known Biological Cause](#), (Feb. 2026).

[3] Amanda Conti, [Analysis: The majority of novel drugs approved by FDA rely on evidence from a single pivotal trial](#), AgencyIQ (Apr. 4, 2026).

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