SOUNDING BOARD

One Pivotal Trial, the New Default Option for FDA Approval — Ending the Two-Trial Dogma

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Since 1997, the Food and Drug Administration (FDA) has retained statutory authority to grant marketing authorizations on the basis of a single adequate and well-controlled study in combination with confirmative evidence.[1] Confirmative evidence can include mechanistic science, data from a related indication, animal models, information from other drugs of the same class, real-world evidence, or a second adequate and well-controlled study. This flexibility has been applied in parallel with a number of other agency-wide efforts to speed drugs to market — including the breakthrough program designation, accelerated approval, and priority review pathways — but has also been extended to drugs receiving traditional approval after standard review times. As such it is not purely overlapping with these other efforts.

The FDA has demonstrated disease-by-disease flexibility and has granted approvals based on a single premarket study with confirmatory evidence. In some fields, such as oncology, single trials have supported the majority of drug approvals. However, although we have exercised flexibility in the past, there remains confusion from manufacturers regarding settings in which a single trial will be accepted. Moving forward, we are announcing that a one-trial requirement will be the FDA's new default standard. This reform is being rolled out synchronously with the agency's postmarket initiative to collect robust data on all drugs and devices.

The FDA's historical reliance on two clinical trials rather than one was intended to provide credible causal evidence that a therapy could improve clinical outcomes with acceptable safety in a world where biologic understanding was more limited than it is today. From a statistical perspective, if one tests inert substances — those unlikely to improve or harm health — two trials reduce the chance of a type 1 error favoring the product (finding a difference when one does not exist) from 250 in 10,000 to 6 in 10,000. This happens for the simple reason that one must be lucky twice. Yet modern drug development establishes credibility in multiple ways, relying on both statistical and biologic inferences. Scientific laboratories and the industry go to great pains to elucidate the precise mechanism of action of a product. Requiring two clinical trials has a powerful theoretical basis to reduce false-positive conclusions in a world where developers test inert substances (or substances with nearly no preclinical promise) without the ability to assess their effect on biomarkers or intermediate end points. Yet in the modern world, as drug discovery becomes increasingly precise and scientific, the FDA considers not just effects on survival, but biochemical and intermediate changes that tell a complete biologic story: does this drug actually work? In this setting, overreliance on two trials no longer makes sense. Two trials should be seen as just one of many interlocking facets of clinical credibility, and in 2026 there are powerful alternative ways to feel assured that our products help people live longer or better than requiring manufacturers to test them yet again.

A few other factors that contribute to an overall picture of credibility include the magnitude of the effect, the use of a contemporary control group (versus a historical one[2]), the nature of the control group (is it the best available therapy?[3]), the prespecification of a hypothesis, the choice of a primary end point, the concordance with biologic correlates (including evidence of alteration of an in vivo target), alignment of intermediate end points, statistical power, blinding, concealment, independent review, whether post-protocol therapy[4] is on par with the U.S. standard of care, the use of concomitant therapy, inclusion criteria, exclusion criteria, randomization, run-in periods, how missing data are handled, and many additional factors.[5] Increasingly, many of these factors

are captured in a Bayesian (as opposed to frequentist) interpretation of trials, and the FDA has guidance in this space.[6]

Our move to change the FDA's default position from two clinical trials to one will substantially reduce costs for sponsors and will speed drugs to market. Estimates suggest that the cost of a single pivotal study may range from 30 million to 150 million dollars.[7] Such trials may require years to complete, further increasing the average time to bring a new drug to market, which easily exceeds 7 years.[8] Lowering capital costs for drug developers may remove a persistent argument in justification of lofty and rising drug prices for everyday Americans — the onerous cost of research and development.

When drugs are transformative, the effect of novel therapies can be evident with confirmatory evidence. For instance, the approval of imatinib in 2001 was based on hematologic response — a surrogate end point relying on blood counts. Yet the mechanistic science was so sound and the clinical effect of the drug so robust that we can see it in national cancer data — specifically, SEER data show a dramatic change in mortality corresponding to the adoption of the therapy,[9] and Swedish data show a restoration of life expectancy.[10] When a drug is a game-changer, you can see the effect from space.

Critics may argue that our initiative means that the FDA is relaxing its standards and will now permit ineffective or even harmful products on the U.S. market. This is incorrect. First, the FDA has never been perfect, and even with a default requirement of two trials, the FDA has approved numerous products that were later found to have serious safety concerns or lack efficacy. Second, as we note, the number of clinical studies is no safeguard against valid inference if all other aspects of trial design are deficient. If the control arm is substandard, the end points dubious, the statistical plan generated post hoc, the power inadequate, or all of the above, erroneous conclusions may be reached even with two, three, or four studies. Ignoring all the puzzle pieces that result in credibility — and being categorically opposed to reducing the requirement from two clinical trials to one — is an unjustified and entrenched position. In fact, our proposal for a default of one robust and sound clinical study may even enhance the FDA's standards and reduce the risk of approval of products that may later need to be withdrawn, since greater attention will be placed on the one trial. Although the FDA reviews clinical trial protocols, our approvals have been faulted for permitting manufacturers to compare novel drugs with control drugs that are no longer used by the American people,[3] for instance. Instead of prioritizing finite reviewer time reading and assessing two or more pivotal trials, we will focus our energies on ensuring that the one clinical trial we require provides the most up-to-date and useful information for American patients.

Others may note that changing the default FDA stance is a modest proposal, given that the FDA has already demonstrated flexibility. Again, we disagree. A wide body of literature suggests that default options anchor individuals and institutions psychologically,[11] and we believe that formally articulating the FDA's new position will spur biomedical innovation.

Finally, changing the default option does not mean the FDA will never require two studies. 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, additional adequate and well-controlled studies may be required. The FDA will always reserve the right to demand the appropriate scientific study within the bounds of U.S. law.

Going forward, the FDA's default position is that one adequate and well-controlled study, combined with confirmatory evidence, will serve as the basis of marketing authorization of novel products. The FDA will carefully examine all aspects of study design with particular focus on controls, end points, effect size, and statistical protocols. Without examination of the quality of a study, two trials may even provide a false assurance. The FDA expects a surge in drug development in response to our initiative.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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