CENTER FOR
Science IN THE
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Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: FDA Draft Guidance on Substantial Evidence of Effectiveness for Human Drug and Biological Products (Docket No. FDA-2019-D-4964)

Dear Dockets Management Staff,

The Center for Science in the Public Interest (CSPI) respectfully submits these comments regarding the Food and Drug Administration's (FDA's) draft guidance titled "Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products."[1] CSPI is a non-profit consumer education and advocacy organization that has advocated for evidence-based policies to improve health, nutrition, and food safety since 1971. CSPI is an independent organization that does not accept any corporate funding.

We appreciate the agency issuing a draft guidance to clarify, in part, how drug developers "can rely on one scientifically rigorous adequate and well-controlled clinical investigation with confirmatory evidence to satisfy the statutory substantial evidence of effectiveness standard."[1]

The new draft guidance explains that the substantial evidence standard can be met either with one adequate and well-controlled trial plus confirmatory evidence or with more than one adequate and well-controlled trial.[1] The draft guidance then lays out two ways of meeting approval standards with only a single trial: 1) "evidence from an adequate and well-controlled trial plus a source of strong confirmatory evidence," and 2) "evidence from a highly persuasive adequate and well-controlled trial plus early-phase confirmatory evidence."[1]

In fact, this draft guidance is pared back from former agency leaders' announcement on February 19, 2026, in the *New England Journal of Medicine* that "a one-trial requirement will be the FDA's new default standard."[2] In effect, the draft guidance retreats from the journal article's insistence on a one-trial default standard to an approach where using one trial is only one of several options to satisfy the statutory requirement of "substantial evidence of effectiveness" to secure drug approval. Nonetheless, we remain concerned about several elements of the draft guidance that threaten approval standards, are internally inconsistent, or contradict the agency's previously stated positions.

We recognize that, for certain drug development programs for rare diseases or other life-threatening conditions, running two trials may not be feasible or ethical. However, this draft guidance separately addresses regulatory flexibility for these conditions, including in trial design, endpoint selection, statistical analysis, and sources and strengths of confirmatory evidence.

In fact, to a large and increasing extent, FDA has been approving novel therapeutics based on a single clinical trial. An analysis of all 188 FDA-approved novel therapeutics from 2005 to 2012 found that 74 of the 201 approved indications (36.8%) relied on one pivotal trial.[3] From 2016 to 2024, FDA approval of

novel drugs trended even more towards reliance on fewer trials, such that the mean number of trials for approved novel therapeutics declined significantly from 3.41 in 2016 to 1.39 in 2024.[4] By 2024, 69% of all new drugs (n=50) were approved on the basis of a single pivotal study.[4] If the FDA intends to prompt a reduction in the number of pivotal trials, this draft guidance seems late to the game.

Our comments are as follows:

1. **The FDA's greater emphasis on relying on one-trial plus confirmatory evidence is concerning.**

While the draft guidance leaves intact an option to conduct more than one pivotal trial, in a departure from previous agency guidance,[5] the one-trial option is discussed before the two-trial option, conveying an implicit agency preference. For the reasons discussed in this comment, we recommend that the two-trial option be discussed first.

A fundamental deficit in both the *New England Journal of Medicine* article and the draft guidance is the failure to even present data that might justify this switch in approach. The fundamental question is how often the results of pivotal trials diverge. If they rarely do so, perhaps moving to the one-trial paradigm could be justified in certain circumstances on efficiency grounds. Conversely, if there is significant disagreement between pivotal studies, a two-trial approach would be justified. Although the agency is in possession of such data (and external parties are not because they have no trial results for unapproved drugs), it has not provided the very data that might form the justification for its policy.

We have previously written, in response to the *New England Journal of Medicine* article, that not only do two trials mitigate the possibility of approving drugs that do not work (it is impossible to identify a false-positive study if you only have one study), two trials may also permit the approval of a drug whose "first" trial was negative (false negatives).[6] Independent investigators have examined pivotal trials for 21 drugs that were approved by the FDA during the 2018–2021 period for which at least one pivotal trial showed null findings for a primary efficacy endpoint. The agency justified the approval of 13 of these drugs (62%) at least partially on the basis of positive findings in another pivotal trial.[7] Without a second trial, these 13 recently approved, presumably efficacious drugs may never have been approved.

2. **The definitions of "confirmatory evidence" and "strong confirmatory evidence" are vague and subjective.**

Under Section IV.A.1 of the draft guidance, FDA gives examples of "strong confirmatory evidence" that, combined with evidence from "an adequate and well-controlled trial," could justify approval. Such examples include trial data from "related diseases or conditions or for related products" and a "different but closely related indication."[1] These characterizations are vague and open to interpretation, opening the door for companies to press for FDA to adopt overly inclusive definitions of these terms as they push for their product to be approved.

The agency uses "infections at different anatomical sites caused by similar pathogens against which the drug is active" as an example of a "different but closely related disease."[1] Up until now, FDA has generally required separate trials for each site for which approval was sought. FDA's label for daptomycin highlights the limitation of this approach, as the antibiotic, approved by the FDA for skin and bloodstream infections, lacked effectiveness in treating patients with community-acquired pneumonia.[8]

We would also caution against relying on trial results from the same pharmacological class as confirmatory evidence, as even drugs with similar mechanisms of action can yield differing results. For example, the American Diabetes Association recommends sodium-glucose cotransporter 2 (SGLT2) inhibitors, such as canagliflozin and dapagliflozin, for glycemic management and prevention of hospitalization in adults with type 2 diabetes who have heart failure.[9] In contrast, for licogliflozin, which relies partially on the same mechanism of action, a phase 2 trial could not conclusively determine whether the drug reduced glycated hemoglobin (HbA1c) compared to placebo in patients with type 2 diabetes due to low sample size, and the sponsor ultimately paused development of this drug candidate without submitting it for FDA approval.[10,11] FDA would never approve a product based on efficacy evidence from a drug in the same pharmacological class alone, so considering this to be "strong confirmatory evidence" seems out of line with prior practice. It is also an incentive for industry to produce closely related products ("me-too") drugs, reducing innovation.

3. **FDA should clarify expectations for a highly persuasive trial and define "early-phase" confirmatory evidence.**

Section IV.A.2 provides a six-point list of what would constitute a highly persuasive trial (which would then only need to be combined with "early-phase" confirmatory evidence to secure approval). Assumedly, any one of these criteria is insufficient on its own, so FDA should clarify that all of the criteria listed must be met for a trial to be considered "highly persuasive."

In addition, the term "early-phase confirmatory evidence" is not defined in the draft guidance, which could lead to confusion in regulatory submissions and open the door for sponsors to introduce data of only peripheral significance.

4. **The draft guidance assumes knowledge not yet in evidence.**

One problem with using the draft guidance as the basis for a development program is that one simply cannot know a priori whether one's pivotal trial will be "highly persuasive," merely "adequate and well-controlled," or even negative, until the study is complete. Thus, despite the agency's recommendation for sponsors to discuss their approach to meeting the efficacy standard before pivotal trial initiation, sponsors have no assurance that their confirmatory evidence will prove adequate or that the agency will not require additional studies. Instead, the agency's increased emphasis on relying on one trial and confirmatory evidence may set an expectation that this evidence would be sufficient regardless of the persuasiveness of the outcome. Similarly, an adequately designed trial may not yield highly persuasive results or may be subject to poor execution or even fraud, which would not be known until after the fact. The need to conduct an additional trial or collect additional confirmatory evidence after the initial (single) trial is complete would lengthen development times, reduce product profitability as patent- and exclusivity-protected time are reduced, and potentially delay patient access to effective drugs. For small companies, conducting these trials in sequence may not be feasible.

Moreover, because the agency would have committed to accepting one trial at the outset of a development program, sponsors facing the prospect of a new pivotal trial are likely to pressure FDA to approve based on the single trial and will use the vagueness of key terms described above to make their case.

5. **FDA must place guardrails on extrapolation from one circumstance to another.**

Section IV.C, which focuses on extrapolation to a new population, dosage, regimen, or route of administration based on previously known effectiveness states that such extrapolation should be "scientifically justified and legally permissible."[1]

Not only are these terms not well-defined (e.g., what are the legal provisions that govern "legally permissible"?), but we question the agency's example that effectiveness of a pediatric drug can be concluded based on the known effectiveness of the drug in adult populations. We urge the agency to consider the potential harms to patients if pediatric drugs are approved without at least some clinical investigation in children.

6. **FDA concedes the benefit of two trials.**

In at least two instances, the draft guidance acknowledges that relying on two trials to support drug approvals can be particularly valuable. In Section III.E, the agency states that, "in a program with multiple adequate and well-controlled trials, an adequate and well-controlled trial that produces an estimate of no effect or even harm…could call into question the results from additional adequate and well-controlled trials..."[1] (This is the "false-positive" situation we described earlier.) Here, despite the foregrounding of the one-trial options, the agency is acknowledging the value of the age-old scientific concept of replication, a tenet of "gold standard science" outlined in the May 2025 Executive Order 14303.[12]

In addition, FDA acknowledges under Section IV.B that "positive results from two nonidentical trials may be more persuasive, as unrecognized flaws may be less likely to impact the outcome of both trials."[1] This in effect acknowledges that two trials can also help address the "false-negative" problem we identified earlier. These arguments are persuasive, but the agency fails to follow them to their logical conclusions.

Conclusion

CSPI opposes any shifts in the regulatory standard to a one-trial default, and, while the draft guidance stops short of directly articulating such a position, the agency's preferences are implicit and clear. The draft guidance thus needs significant revisions to ensure that it aligns with the agency's public health mission.

We ask the agency to provide supporting evidence to justify its decision, better define terms in the draft guidance, and consider the potential risks of extrapolation based on known effectiveness. Two clinical trials not only serve to independently substantiate trial results (as the agency even acknowledged in the draft guidance) but also support the agency's public health mission of ensuring the efficacy of human drug and biological products before they are released to the American public.

Sincerely,

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