



December 18, 2023

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, Maryland 20852

Re: FDA-2023-D-2318-0003
Filed electronically at <http://www.regulations.gov>

Dear Commissioner Califf,

Thank you for the opportunity to provide comments to the Food and Drug Administration (FDA) on the following draft guidance issued in September 2023:

- *Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence*

Arnold Ventures is a philanthropy dedicated to investing in evidence-based policy solutions that maximize opportunity and minimize injustice. We work to develop evidence to drive reform across a range of issues including health care, education, and criminal justice. Our work within the health care sector is driven by the recognition that the system costs too much and fails to adequately care for the people it serves.

Background

The Food and Drug Administration Modernization Act of 1997 (Pub. L. 105–115) outlines that FDA may consider data from (1) one adequate and well-controlled clinical investigation (herein referred to as “the controlled clinical investigation”) and (2) confirmatory evidence (obtained prior to or after such investigation) to establish substantial evidence of effectiveness for products approved under Section 505(d) of the Federal Food, Drug, and Cosmetic Act.

Use of single pivotal trials. Between 2005 and 2012, FDA approved 188 novel therapeutics for 206 indications. Over a third of these indications were approved based on a single pivotal trial.¹ By 2020, more than half of novel therapeutics approved were supported by evidence from a single pivotal trial.²

While there has long been focus on the importance of clinical research to support evidence of drug effectiveness,³ any single study can be wrong by chance alone.⁴ FDA previously outlined⁵ concerns that can lead to flawed conclusions, including:

¹ JAMA. 2014 Jan 22-29; 311(4): 368–377.

² JAMA Netw Open. 2022 May; 5(5): e2212454.

³ JAMA Oncol. 2018 Jul; 4(7): 993–994.

⁴ PLoS Med. 2005 Aug; 2(8): e124.

⁵ Food and Drug Administration. (1998, May). Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products. <http://www.fda.gov/cder/guidance/index.htm>.



- Design and conduct of any clinical trial may be subject to systematic and conscious biases, and;
- Statistical analysis of all clinical trials implies an error rate in efficacy,⁶ and independent substantiation protects against an erroneous conclusion that a treatment is effective.

False positive findings are more likely when the study sample size and treatment effect sizes are smaller, but also when there is greater flexibility in study definitions, monitoring of study participants, and analyses.⁷

Definition of confirmatory evidence. FDA finalized guidance in 1998 with the types of evidence that could be considered confirmatory evidence.⁸ The latest draft guidance expands the types of confirmatory evidence accepted, which can contribute to more drugs on the market with less evidence of safety and efficacy available.

Without independent substantiation of patient benefits and harms of the interventions tested and reviewed by the FDA, there will continue to be bias in study design, conduct, and analysis of trial results that are not generalizable; and unconfirmed positive results likely to be due to chance alone as noted in the previous FDA guidance.⁹

We recommend the following changes to this draft guidance that address both the use of a single pivotal trial and confirmatory evidence generation:

1. Clarify that pre-clinical information collected before the controlled clinical investigation begins cannot demonstrate confirmatory evidence of patient benefit and harm after the intervention is studied.
2. Require clinical trial sponsors to publicly post sufficient details of design, conduct, and analysis of the controlled clinical investigation to allow evaluation by the scientific community.
3. Require a product's label to state when direct evidence of patient benefit is not available. This applies to circumstances when a controlled clinical investigation ends, and confirmatory evidence of patient efficacy and safety is not yet complete.

Recommendations

1. *Clarify that pre-clinical information collected before the controlled clinical investigation begins cannot demonstrate confirmatory evidence of patient benefit and harm after the intervention is studied.*

We recommend that FDA exclude mechanistic or pharmacodynamic evidence in its definition of confirmatory evidence. As described in this draft guidance, this evidence type would represent testing in a test tube, culture dish, or otherwise outside of humans. While this type of testing gives a stronger rationale for a proposed mechanism of action for a drug, it does not confirm evidence of patient benefit and harm after a clinical investigation. Therefore, mechanistic or pharmacodynamic evidence should be outside of scope of the definition of confirmatory evidence as they inform but do not confirm benefits and harm in humans.

⁶ Controlled Clinical Trials. 1997 Dec; 18(6):550-556.

⁷ Friedman, L. M., Furberg, C. D., DeMets, D.L. (1998). Fundamentals of clinical trials. 3rd ed. Springer.

⁸ See footnote 5.

⁹ See footnote 5.



Relevant animal models are proposed by FDA as a type of confirmatory evidence. However, we do not think these models should be used to confirm a clinical investigation of effectiveness. These types of information are often necessary in order to file an Investigational New Drug Application to support first use in humans, but do not provide confirmation of efficacy and safety in humans. As required, drug sponsors must include in their marketing submissions a description and analysis of all data or information relevant to an evaluation of the safety and effectiveness of the drug product, from any source, foreign or domestic, to avoid selecting only those sources that favor a conclusion of effectiveness.

FDA states in its draft guidance that the finding of substantial evidence of effectiveness alone is not sufficient for FDA approval. Therefore, we recommend that FDA include in final guidance that evaluating whether a drug is safe involves weighing whether the benefits of the drug outweigh its risks under the conditions of approval. Single studies typically enroll smaller samples of patients, so the picture of drug safety is incomplete given that serious adverse events may be of lower frequency and would influence the overall assessment of benefits and harms.¹⁰ This is a key concept¹¹ that (1) highlights the significance of additional trials to identify a more complete picture of adverse drug reactions, and (2) provides an additional reason why more than one trial to establish drug safety and efficacy should be standard practice.

Additionally, the definition of confirmatory evidence should be limited to controlled, clinical research in humans. Specifically, evidence from other products in the same pharmacological class should be limited to situations when two drugs have the same mechanism of action, and impact the same clinical outcomes, with no difference in harms, which is consistent with prior guidance.¹²

2. Require clinical trial sponsors to publicly post sufficient details of design, conduct, and analysis of the controlled clinical investigation to allow evaluation by the scientific community.

Substantial evidence of effectiveness is generated by adequate and well-controlled clinical investigations, and collected by qualified experts, to evaluate drug effectiveness. We recommend that final guidance make clear that such investigations deploy and maintain a valid comparison with adequate controls to provide a quantitative assessment of treatment effect. Valid comparisons take into consideration the duration of treatment periods, whether treatments are parallel or sequential, and whether the sample size changes after a predetermined interim analysis. More information should be provided in final guidance that requires greater transparency while the controlled clinical investigation is underway. This requirement fulfills public expectations that fair and responsible conclusions are evaluated.

Additionally, consistent with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), there is a need for good clinical practice as a guideline for clinical trial conduct. Good clinical practice was included in 1998 final guidance¹³ but omitted from this draft guidance. To achieve a high level of conduct, studies supporting claims are ordinarily conducted in accordance with good clinical practice. We recommend that FDA recognize ICH Guideline for good clinical practice E6(R2) in final guidance.

¹⁰ BMJ. 1995 Sep 2; 311(7005): 619–620.

¹¹ Postgrad Med. 2011 Sep; 123(5): 194–204.

¹² See footnote 5.

¹³ See footnote 5.



3. *Require a product's label to state when direct evidence of patient benefit is not available. This applies to circumstances when a controlled clinical investigation ends, and confirmatory evidence of patient efficacy and safety is not yet complete.*

We recommend that natural history evidence, real world evidence, and evidence from expanded access use of an investigational drug be limited in use as confirmatory evidence to situations where (1) it is listed by ICH-E10, and (2) valid conclusions can be drawn to independently substantiate an adequate and well-controlled clinical investigation. We question the utility of these types of confirmatory evidence of efficacy and safety in patients because these types of information are more difficult to control and slower to mature when compared to a second well-controlled trial that provides independent substantiation of trial results. As the pace of clinical care continues to evolve, we expect that the relevance of these types of confirmatory evidence can diminish over time. Therefore, we recommend that FDA incorporate by reference conditions listed in ICH for the aforementioned types of information.

Additionally, there is evidence that labels for drugs reviewed under the accelerated approval pathway often lack adequate information for clinical decision-making.¹⁴ This raises concerns for the integrity of confirmatory evidence when drugs approved via the accelerated approval pathway cannot verify benefits for patients.¹⁵ We commented previously on FDA draft guidance for clinical trial considerations to better support evidence generation under the accelerated approval pathway.¹⁶

Conclusion

Thank you again for the opportunity to comment and for your important work ensuring the safety and efficacy of human drugs and biological products. We are prepared to assist with any additional information needed to address these comments in final guidance to industry. Comments were prepared by Katherine Szarama, Ph.D. Director of Health Care at Arnold Ventures, with assistance from John Powers, MD.

Please contact Mark E. Miller, Ph.D. Executive Vice President of Health Care at Arnold Ventures at mmiller@arnoldventures.org or Andrea Noda, MPP, Vice President of Health Care at anoda@arnoldventures.org with any questions.

Sincerely,

Andrea Noda

¹⁴ Pharmacotherapy 2023 Apr;43(4):300-304.

¹⁵ JAMA Intern Med. 2019 Jul;179(7):906-913.

¹⁶ [Arnold-Ventures-Comments-on-FDA-Accelerated-Approval-Draft-Guidance.pdf](#)