Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

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Revision 1

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Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION

This document is intended to provide guidance to applicants planning to submit new drug applications (NDAs), biologics license applications (BLAs), or supplements to NDAs or BLAs that require the demonstration of substantial evidence of effectiveness. This guidance revises the draft guidance for industry of the same name issued in December 2019. When finalized, this guidance will replace the 1998 guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998).[2]

Advances in our understanding of biological processes and the increasing availability of high-quality data have transformed the evidentiary landscape for drug development. Given these advances, this guidance clarifies how sponsors can rely on one scientifically rigorous adequate and well-controlled clinical investigation with confirmatory evidence to satisfy the statutory substantial evidence of effectiveness standard as defined in section 505(d) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). This guidance highlights that there are various ways to provide substantial evidence and emphasizes the many factors that can impact the strength of evidence of effectiveness for a drug.[3] These factors include important elements of the design, conduct, and analysis of the adequate and well-controlled clinical investigation(s), the clinical and statistical persuasiveness of results, and the characteristics of the overall development program. Whether sponsors have demonstrated substantial evidence will depend on the strength of the evidence provided.

[1] This guidance has been prepared by the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research and the Oncology Center of Excellence at the Food and Drug Administration.

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[3] For the purposes of this guidance, the term *drug* or *drugs* refers to human drugs and biological products unless otherwise specified.

The finding of substantial evidence of effectiveness is necessary but not sufficient for FDA approval. The approval decision also requires a determination that the drug is safe for the intended use and that the benefits outweigh the risks.[4] As such, there must be sufficient safety data for FDA to consider the drug's safety profile. As all drugs have adverse effects, evaluating whether a drug is safe involves determining whether the benefits of the drug outweigh its risks under the conditions of use defined in labeling. Uncertainties about benefits and risks are also considered when making an approval determination; a drug with greater risks may require a greater magnitude and certainty of benefit to support approval. This benefit-risk assessment[5] and other determinations necessary for approval are outside the scope of this guidance.

Sponsors should discuss their anticipated approach to demonstrating substantial evidence of effectiveness with FDA early in development, such as at a pre-investigational new drug application meeting, and no later than at an end-of-phase 2 meeting.[6] When meeting with FDA, sponsors should provide a scientific justification for their proposed approach. Ultimately, whether substantial evidence of effectiveness has been demonstrated will depend on FDA's review of the marketing application.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. LEGAL STANDARD OF EFFECTIVENESS FOR DRUG AND BIOLOGICAL PRODUCTS

For FDA to approve a drug under section 505 of the FD&C Act, applicants must provide, among other things, substantial evidence of effectiveness. As stated in section 505(d), substantial evidence is defined as:

> evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof. If [FDA] determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or

[4] Section 505(d) of the FD&C Act (21 U.S.C. 355(d)).

[5] See the guidance for industry *Benefit-Risk Assessment for New Drug and Biological Products* (October 2023).

[6] See the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (September 2023). When finalized, this guidance will reflect FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

> after such investigation) are sufficient to establish effectiveness, [FDA] may consider such data and evidence to constitute substantial evidence[.][7]

To establish a drug's effectiveness, it is essential to distinguish the effect of the drug "from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation."[8] This is the basis for the statutory requirement that approval be based on adequate and well-controlled investigation(s), as well as the basis for FDA's regulations describing the characteristics of such investigation(s), i.e., elements that are generally intended to minimize bias and permit a valid comparison with a control to provide a quantitative assessment of drug effect. FDA's regulation at 21 CFR 314.126(b) describes characteristics of an adequate and well-controlled clinical investigation, including choice of control, method of participant selection and assignment to treatment (e.g., randomization), adequate measures to minimize bias (e.g., blinding), well-defined and reliable assessment of individuals' response (e.g., efficacy endpoint), and adequate analysis of the clinical investigation's results to assess the effects of the drug (e.g., particular statistical methods).

Under section 351(a) of the Public Health Service Act (PHS Act) (42 U.S.C. 262(a)), licenses for biological products have been issued only upon a showing that the products are "safe, pure, and potent." Potency has long been interpreted to include effectiveness (21 CFR 600.3(s)). FDA has also generally considered *substantial evidence* of effectiveness to be necessary to support licensure of a biological product under section 351(a) of the PHS Act.[9]

A sponsor may also leverage the known effectiveness of an approved drug when it is scientifically justified and legally permissible without needing to conduct additional adequate and well-controlled clinical investigations (see section IV.C).[10]

III. FACTORS IMPACTING THE STRENGTH OF EVIDENCE OF EFFECTIVENESS

[7] Section 505(d) of the FD&C Act (21 U.S.C. 355(d)).

[8] 21 CFR 314.126(a).

[9] In 1972, FDA initiated a review of the safety and effectiveness of all previously licensed biological products. The Agency stated then that proof of effectiveness would, with limited exceptions, consist of controlled clinical investigations as defined in the provision for "adequate and well-controlled studies" for new drugs (21 CFR 314.126) (see former 21 CFR 601.25(d)(2) (2015) (revoked as no longer necessary, 81 FR 7445 (Feb. 12, 2016))). We note that, in section 123(f)) of the Food and Drug Administration Modernization Act of 1997 (Pub. L. 105-115), Congress also directed the Agency to take measures to "minimize differences in the review and approval" of products required to have approved BLAs under section 351 of the PHS Act (42 U.S.C. 262) and products required to have approved NDAs submitted under section 505(b)(1) of the FD&C Act (21 U.S.C. 355(b)(1)).

[10] There are certain regulatory considerations that apply when an applicant leverages certain types of information for approval of certain applications (e.g., reliance on a previous finding of safety and effectiveness for a drug the applicant does not own or to which it has no right of reference for approval of a 505(b)(2) application). See footnote 34.

The strength of evidence of effectiveness can be impacted by many factors, such as key clinical trial[11] design elements (e.g., control, population selection, randomization, blinding, endpoint), quality of trial conduct (e.g., completeness of follow-up), aspects of the trial analysis (e.g., prespecification, analysis assumptions), the clinical and statistical persuasiveness of trial results, and aspects of the overall drug development program. This section highlights key factors but does not provide an exhaustive description of all factors that can impact the strength of evidence.

A. Trial Design

Design elements should be selected to help ensure a trial is adequate and well-controlled and can distinguish the effect of the drug from other influences (see section II). Two critical elements are the choice of control[12] and the method of assignment to treatment (e.g., randomization). Generally, the following types of controls are recognized in trials designed to allow for well-supported conclusions about effectiveness:[13] placebo concurrent control, dose-comparison concurrent control, no-treatment concurrent control, active treatment concurrent control, and historical control (a type of external control). Establishing superiority to a randomized concurrent control group (whether an active control or placebo) generally provides strong evidence of effectiveness.

Other types of designs can support effectiveness in certain circumstances. For example, designs intended to show non-inferiority (NI) against an active control can be credible and appropriate in situations in which the active control has shown a consistent and large effect in prior superiority trials conducted in a patient population and clinical setting similar to the trial being planned. NI trials provide relevant comparisons against standard of care and can facilitate collection of long-term controlled data to inform the benefit-risk assessment. However, NI trials depend on assumptions about the anticipated effect of the active control in the trial. Because an NI demonstration could mean either that both drugs are effective or that both drugs are not effective in the trial, the strength of evidence from an NI trial can vary considerably depending on the level of confidence that the untested assumptions hold and on the selected NI margin, including its relative magnitude compared with the assumed effect of the active control.[14]

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[11] For the purposes of satisfying the substantial evidence of effectiveness standard, adequate and well-controlled clinical investigations can be interventional (clinical trials) or noninterventional (observational studies). The considerations in this document focus primarily on clinical trials. Therefore, this guidance uses the terms *clinical trial(s)* or *trial(s)* in many places. This usage does not imply that the term clinical investigation as used in section 505(d) of the FD&C Act is limited to clinical trials. For considerations regarding noninterventional studies, see the guidance for industry *Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products* (August 2023), and the draft guidance for industry *Real-World Evidence: Considerations Regarding Non-Interventional Studies for Drug and Biological Products* (March 2024). When final, this guidance will represent the FDA's current thinking on this topic.

[12] For additional considerations about the choice of control, see the ICH guidance for industry *E10 Choice of Control Group and Related Issues in Clinical Trials* (May 2001).

[13] See 21 CFR 314.126(b)(2) and 50 FR 7452, 7487 (February 22, 1985).

[14] See the guidance for industry *Non-Inferiority Clinical Trials to Establish Effectiveness* (November 2016).

As another example, although externally controlled trials[15] often have a high potential for bias, they can generate evidence of effectiveness in certain circumstances. Many externally controlled trials compare a group of trial participants receiving the drug with a defined group of people external to the trial, either treated with another therapy or untreated, from an earlier time (historical control) or from the same time period but not enrolled in the trial. In other situations, the external control may not involve a defined group but instead consist of well-established and broadly accepted evidence of the natural history[16] of the disease, which could support a conclusion that an outcome (e.g., substantial reduction in tumor size) would not have occurred in the absence of an intervention.[17] Because of the lack of randomized treatment assignment, differences between the trial population and the external control population (e.g., baseline participant characteristics, baseline concomitant treatments, definition of the start of the follow-up period, endpoint ascertainment, knowledge of treatment) can lead to differences in outcomes that are unrelated to the drug. Despite these challenges, support for effectiveness can emerge from externally controlled trials when (1) the natural history of a disease is well defined, (2) the external control population is very similar to that of the treatment group, (3) concomitant treatments that affect the outcomes of interest are very similar between the external control population and the trial population, (4) the endpoint is objective and meaningful, with comparable definition and ascertainment across the populations, (5) the start of the observation period is comparable between the populations, and (6) the estimated treatment effect based on the prespecified statistical analysis is so large that it is unlikely to be fully attributable to bias.

Another important design element is the choice of trial endpoints, particularly the primary endpoint. Effectiveness is often supported by evaluation of a clinical endpoint, which is a precisely defined variable intended to describe or reflect how a patient feels, functions, or survives.[18] Examples of clinical endpoints include survival time, risk of clinical outcomes such as major adverse cardiovascular events (MACE), and patient-reported outcome (PRO)-based endpoints assessing patient functioning or symptom severity.[19] Use of a clinical endpoint is preferred when feasible. An alternative approach is to use a surrogate endpoint, which is not a direct measure of how patients feel, function, or survive but is intended to predict clinical benefit, i.e., to predict a favorable drug effect on a clinical endpoint. Surrogate endpoints can

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[15] For detailed considerations about externally controlled trials, see the draft guidance for industry *Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products* (February 2023). When final, this guidance will represent the FDA's current thinking on this topic.

[16] See the draft guidance for industry *Rare Diseases: Natural History Studies for Drug Development* (March 2019). When final, this guidance will represent the FDA's current thinking on this topic.

[17] See ICH E10.

[18] See the BEST (Biomarkers, EndpointS, and other Tools) Resource at https://www.ncbi.nlm.nih.gov/books/NBK338448/.

[19] Clinical outcome assessments such as PROs should be fit for purpose and appropriately incorporated into endpoints. See the guidance for industry, Food and Drug Administration Staff, and Other Stakeholders *Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments* (October 2025) and the draft guidance for industry, Food and Drug Administration Staff, and Other Stakeholders *Patient-Focused Drug Development: Incorporating Clinical Outcome Assessments Into Endpoints for Regulatory Decision-Making* (April 2023). When final, this guidance will represent the FDA's current thinking on this topic.

often be measured earlier or more precisely than clinical endpoints, potentially allowing for shorter or smaller studies. However, use of a surrogate endpoint requires an appropriate justification, including scientific evidence to support an understanding of the relationship between drug effects on the surrogate endpoint and drug effects on a relevant clinical endpoint. Surrogate endpoints that are reasonably likely to predict clinical benefit can be used to support accelerated approval when specific criteria are met.[20] Surrogate endpoints that are validated to predict clinical benefit can be used to support traditional approval.[21]

It is important that trial designs provide information that is relevant to patients and prescribers in clinical practice. Eligibility criteria should be selected to reflect the intended-use population, including with respect to age, sex, race, ethnicity, and disease severity, with exclusion criteria used only if scientifically justified (e.g., to avoid certain drug-drug interactions and ensure participant safety).[22] The relevance of results can also be enhanced by design features such as enrollment and retention practices that improve participation and generalizability, selection of a control arm and supportive therapies that reflect current standard of care, visit and endpoint assessment approaches to reduce burden for participants, and use of a prespecified primary endpoint that is meaningful to patients.

There are also many other important design elements that can impact the strength of evidence generated in a trial. These include, for example, the degree of blinding to treatment assignment, choice of drug dosage, selection of clinical trial sites, use of concomitant therapies, trial duration, sample size, adaptive design elements,[23] and approach to ascertain outcomes in participants.

B. Trial Conduct

The quality of trial conduct also impacts the strength of evidence generated by a trial. For example, this includes the maintenance of blinding of trial participants and investigators to treatment assignment in a double-blind design, the maintenance of confidentiality of interim results while the trial is ongoing, the quality of data collection, the extent of adherence to treatment and to the protocol, and the completeness of follow-up of participants, including the amount of and reasons for missing data on key endpoints. Clinical trials should be conducted in accordance with Good Clinical Practice (GCP) standards.[24] Poor execution can render a trial of any design not adequate or not well-controlled and, therefore, unable to contribute to substantial

[20] Note that for accelerated approval, the evidentiary standard still applies—that is, there must be substantial evidence of effectiveness.

[21] See further details about reasonably likely and validated surrogate endpoints in the BEST Resource, and further discussion about reasonably likely surrogate endpoints and accelerated approval in the draft guidance for industry *Expedited Program for Serious Conditions – Accelerated Approval of Drugs and Biologics* (December 2024). When final, this guidance will represent the FDA's current thinking on this topic.

[22] See the guidance for industry *Enhancing Participation in Clinical Trials — Eligibility Criteria, Enrollment Practices, and Trial Designs* (December 2025).

[23] See the guidance for industry *Adaptive Designs for Clinical Trials of Drugs and Biologics* (November 2019).

[24] See the ICH guidance for industry *E6(R3) Good Clinical Practice* (September 2025).

evidence of effectiveness. Examples of this might include (1) a randomized, double-blind, placebo-controlled trial where there is extensive dropout of trial participants and major concerns about bias induced by the missing data; and (2) a randomized, double-blind, placebo-controlled trial in which unblinding is common due to an effect of the drug, and where a treatment effect is found on a primary endpoint that is subject to bias when treatment assignment is known (e.g., distance walked on the 6-minute walk test).

C. Trial Analysis Plan

There are a variety of important statistical considerations in ensuring that trials are adequate and well-controlled and in evaluating the strength of evidence of effectiveness.[25] An adequate and well-controlled trial should have a prespecified primary analysis that is aligned with a clinically meaningful primary estimand.[26] The traditional approach to limiting erroneous conclusions of effectiveness is to select the design and analysis approach such that the type I error probability with respect to the primary estimand is controlled at a prespecified level. It is common to perform hypothesis testing at a one-sided significance level of 0.025 (or two-sided 0.05), where a p-value or confidence limit is used to determine whether the null hypothesis is rejected in favor of an alternative or is not rejected. In certain settings, such as when the prior evidence for the effectiveness of the drug is not strong, FDA may expect a more stringent prespecified significance level (see section IV.A.2). In settings where regulatory flexibility is warranted, FDA may consider flexibility in the significance level expected (see section V.B.1). Bayesian approaches may also be considered. There should be early communication and agreement with FDA at the design stage on the specification of the prior distribution and the success criteria.[27]

The prespecified analysis plan should include appropriate statistical methods. For example, the primary analysis should produce valid estimates and inference for the primary estimand under plausible assumptions[28] and should be prespecified with sufficient detail to allow reproduction of results. Any sources of multiplicity (e.g., multiple doses, multiple primary endpoints) should be handled appropriately.[29] In addition, sensitivity analyses should be planned to explore whether conclusions change under plausible violations in the assumptions of the primary analysis, including missing data assumptions. Supplementary analyses can also be planned to provide further insights into the understanding of the treatment effect.

[25] See the ICH guidance for industry *E9 Statistical Principles for Clinical Trials* (September 1998) for a more detailed discussion of key statistical principles in the design, conduct, analysis, and evaluation of clinical trials.

[26] An estimand is a precise definition of the treatment effect reflecting the clinical question posed by the trial objective. See the ICH guidance for industry *E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials* (May 2021). In some cases, there may be multiple primary estimands. See the guidance for industry *Multiple Endpoints in Clinical Trials* (October 2022).

[27] See the draft guidance for industry *Use of Bayesian Methodology in Clinical Trials of Drug and Biological Products* (January 2026). When final, this guidance will represent the FDA's current thinking on this topic.

[28] For example, assumptions about the underlying missing data mechanism should be documented and scientifically plausible.

[29] See the guidance for industry *Multiple Endpoints in Clinical Trials.*

D. Trial Results

The overall persuasiveness of a trial's results can be influenced by many different considerations. These include the magnitude of the p-value (or of alternative measures such as the posterior probability of effectiveness in a Bayesian analysis), as well as the magnitude and clinical meaningfulness of the effect on the primary endpoint. To contribute to a demonstration of substantial evidence of effectiveness, it is well established that the effect shown in the adequate and well-controlled trial must be, in FDA's judgment, clinically meaningful.[30,31] This determination depends on the relevance of the endpoint (see section III.A) and the magnitude of the estimated treatment effect. For example, in a large trial, a small, statistically significant result may be detected; however, depending on the outcome being evaluated, that small treatment effect may not be clinically meaningful. On the other hand, even small effects may be clinically meaningful when the effect is on survival or irreversible morbidity.

The persuasiveness of the trial results also depends on the findings for additional relevant endpoints, as consistency across endpoints that reflect distinct and meaningful aspects of health can increase confidence in results. In addition, the robustness of findings to violations in assumption of the key analyses is important. For example, sensitivity analyses showing that conclusions hold up on all plausible missing data assumptions help support the strength of evidence from a trial.

E. Aspects of the Overall Development Program

The persuasiveness and interpretation of an individual trial's results should also be considered in the context of the overall drug development program. In many programs, various objectives such as finding an appropriate dose, studying different patient populations (e.g., with greater and lesser disease severity, pediatric and adult populations, pregnant women), or comparing the drug to other therapy will result in more than one trial providing data relevant to the evaluation of effectiveness. The information generated in early-phase trials (e.g., supporting the drug's mechanism and selected dose), as well as any relevant external information (e.g., about the disease pathophysiology and natural history, effects of the drug in related diseases, or effects of drugs with similar mechanisms of action), can inform the expectations that the drug will be effective prior to conducting an adequate and well-controlled trial. Such information is relevant because the probability of erroneous conclusions of effectiveness depends on the prior probability of effectiveness, the power, and the type I error probability.[32]

In assessing the evidence in a drug development program, FDA will carefully evaluate any trial data considered relevant for assessing the effectiveness of the drug. For example, in a program with multiple adequate and well-controlled trials, an adequate and well-controlled trial that

[30] See preamble to FDA final rule on accelerated approval (57 FR 58942, 58944 (December 11, 1992)).

[31] See Warner-Lambert Co. v. Heckler, 787 F.2d 147 (3rd Cir. 1986); E.R. Squibb and Sons, Inc. v. Bowen, 870 F.2d 678, 684 (D.C. Cir. 1989).

[32] See Fleming, TR, 2010, Clinical Trials: Discerning Hype from Substance, Ann Intern Med, 153:400–406.

produces an estimate of no effect or even harm, along with confidence intervals that rule out meaningful effects, could call into question the results from additional adequate and well-controlled trials unless there is a clear and compelling explanation for the differences.

IV. APPROACHES TO MEETING THE SUBSTANTIAL EVIDENCE STANDARD

This section describes various approaches for designing high-quality development programs that can support a demonstration of substantial evidence of effectiveness.[33] With any approach, it is critical to consider the many factors described above that can impact the strength of evidence of effectiveness. Sponsors should discuss their proposed approach with FDA early in development and no later than at the end-of-phase 2 meeting.

A. One Adequate and Well-Controlled Clinical Investigation Plus Confirmatory Evidence

FDA will consider many factors in assessing whether one adequate and well-controlled trial plus confirmatory evidence is sufficient for demonstrating substantial evidence of effectiveness. These factors are expected to include the design, conduct, analysis, and persuasiveness of results of the clinical trial; the source and strength of the confirmatory evidence; disease-specific considerations (e.g., seriousness, unmet need, prevalence); and whether it is ethical and practicable to conduct more than one adequate and well-controlled trial. The strength of the design, conduct, analysis, and results of the single trial will affect the strength of confirmatory evidence needed to establish substantial evidence of effectiveness. Given the lack of additional adequate and well-controlled trials to substantiate results, FDA generally expects that a demonstration of substantial evidence of effectiveness with this approach will involve a highly persuasive trial or a source of strong confirmatory evidence (see discussion in sections IV.A.1 and IV.A.2 below). There may also be specific circumstances where additional regulatory flexibility is considered in use of this approach (see section V). The approach of demonstrating substantial evidence with one adequate and well-controlled trial plus confirmatory evidence should be discussed with FDA prior to initiating the single trial.

1. Evidence from an Adequate and Well-Controlled Trial Plus a Source of Strong Confirmatory Evidence

In some circumstances, substantial evidence of effectiveness may be demonstrated by evidence from a single adequate and well-controlled trial in combination with a source of strong confirmatory evidence. FDA generally expects that such strong confirmatory evidence would come from related adequate and well-controlled trial data, such as trial data in related diseases or conditions or for related products.

[33] Under FDA regulations known as the *Animal Rule*, when it is not ethical or feasible to conduct clinical trials, FDA can allow the use of appropriate animal models to generate evidence to establish effectiveness for products intended to treat or prevent serious or life-threatening conditions caused by exposure to toxic biological, chemical, radiological, or nuclear substances. (see 21 CFR 314.600 through 314.650 for drugs or 21 CFR 601.90 through 601.95 for biological products). The Animal Rule is beyond the scope of this guidance. Additional information about the Animal Rule is available at https://www.fda.gov/emergency-preparedness-and-response/mcm-regulatory-science/animal-rule-information.

As an example, a marketing application for a new indication for an already-approved drug might rely on one adequate and well-controlled trial of the drug for the new indication plus results from the adequate and well-controlled trial(s) that formed the basis of a previous approval for a different but closely related indication. Among the factors critical to determining whether an indication is closely related, and whether a drug's effectiveness for that indication can provide confirmatory evidence, are the degree of similarity in the pathophysiology of the diseases, the degree of similarity in the drug's mechanism of action in the diseases, and the degree of similarity between the efficacy endpoints in the diseases. Examples of when trial data from a related indication may be appropriate for use as confirmatory evidence include when the new indication is a different stage of the same disease (e.g., for initial treatment of a particular type of cancer, where the previously approved indication was for a treatment-refractory form of that cancer) or a different but closely related disease (e.g., infections at different anatomical sites caused by similar pathogens against which the drug is active, diseases with a common precursor targeted by the drug, or diseases with similarities in their underlying pathophysiology).

Confirmatory evidence could also come from adequate and well-controlled trials demonstrating effectiveness of other approved drugs from the same pharmacological class.[34] The ability to use information about drugs in a pharmacological class as confirmatory evidence generally depends on factors such as the degree of similarity of the new drug's mechanism of action to the mechanisms of approved members of the class, the extent to which similar endpoints were measured across the class, the consistency of effects on important endpoints across the class, whether the new drug has similar effects as approved drugs in the class, and the number of approved drugs in the class.

2. Evidence from a Highly Persuasive Adequate and Well-Controlled Trial Plus Early-Phase Confirmatory Evidence

In other circumstances, strong confirmatory evidence may not be available when planning a single adequate and well-controlled trial. In such cases, evidence from a highly persuasive adequate and well-controlled trial will be needed to establish substantial evidence of effectiveness. FDA expects that a single highly persuasive trial will typically:

[34] Reliance on data concerning a different drug to support approval may raise legal and regulatory concerns that will need to be considered in each case. If the applicant owns or has a right of reference to the data concerning the other drug, then the legal and regulatory concerns may be satisfied. If there is not such permission, for an NDA, reliance on FDA's finding of safety and effectiveness for another drug may convert the application to a section 505(b)(2) application. A section 505(b)(2) application is subject to certain legal and regulatory requirements, which can include submission of patent certification(s) or statement(s) and delay in its submission or approval in accordance with the statutory exclusivity provisions, as applicable. See the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999). When final this guidance will represent the FDA's current thinking on this topic. In the biological product context, an applicant cannot rely on FDA's previous determination of safety, purity, and potency for a biological product to support approval of a section 351(a) BLA—the applicant would need to meet applicable requirements under the section 351(k) pathway for such reliance. Instead, a section 351(a) BLA applicant seeking to rely on data concerning a licensed biological product to support approval of its proposed product would need to obtain a right of reference to the relevant data in the application from the application holder. In addition, in certain circumstances, reliance on other data not owned by the BLA applicant and for which the BLA applicant does not have a right of reference may raise additional legal considerations.

- Use a design that provides information that is generalizable and relevant to clinical practice in the United States, such as one that enrolls a broad and representative population across multiple sites, including a sufficient number of U.S. patients if the trial is multiregional, and uses a control arm and supportive therapies that reflect current standard of care

- Use a design and analysis plan intended to provide clinically and statistically highly persuasive results, in that the trial (1) uses a clinically meaningful primary endpoint, such as irreversible morbidity or mortality, and (2) has sufficient power to convincingly demonstrate an effect

  - The appropriate significance level will depend on the prior (i.e., pretrial) probability of the drug being effective; in cases where the prior probability of effectiveness is low (e.g., because the disease pathophysiology and drug mechanism are not well understood), a single trial with hypothesis testing at the common one-sided 0.025 significance level may not adequately limit the probability of false positive effectiveness conclusions.

- Generate primary analysis results that are clinically and statistically highly persuasive based on the clinical meaningfulness of the estimated magnitude of benefit, the associated uncertainty (e.g., confidence interval), and the p-value (or alternative measures such as the posterior probability of effectiveness with a Bayesian approach)

- Generate results that are supportive for distinct prespecified secondary endpoints (e.g., effects on both myocardial infarction and stroke for a drug being studied for cardiovascular benefit)[35]

- Generate results that are largely supportive across important trial subsets (e.g., across subgroups defined by concomitant or prior therapy, disease stage, age, sex, race, or geographic region in a global trial)

- Have high-quality conduct, including comprehensive follow-up and minimal missing data, and demonstrate robustness of results to plausible violations in assumptions

The results from such a highly persuasive trial may render a second trial impractical or unethical. For example, conducting a second trial after a strongly positive, well-conducted trial has demonstrated a substantial decrease in mortality would generally present significant ethical concerns.

If the single trial is adequately designed to provide highly persuasive results, it is expected that the available early-phase information used to support proceeding to such a trial may be able to provide sufficient confirmatory evidence. The final assessment of whether substantial evidence

[35] There also can be cases where a drug shows consistent positive results across different comparisons within a single trial. An example is a 4-arm (2×2 factorial) trial (placebo, drug A, drug B, and drug A + drug B) in which the effectiveness of drug A is supported by two controlled comparisons showing that the combination of drug A + drug B is superior to drug B alone and drug A is superior to placebo.

of effectiveness has been demonstrated will depend on the persuasiveness of the single trial results, including the characteristics discussed above, and the sufficiency of the confirmatory evidence.

B. More than One Adequate and Well-Controlled Clinical Investigation

Substantiation of results across independent, adequate and well-controlled trials can help provide strong evidence of effectiveness. Multiple adequate and well-controlled trials within a development program can have identical or different designs. Although positive results from two identically designed trials can provide substantial evidence of effectiveness, the conclusions from precisely replicated trials (or from a single trial) may be vulnerable to any systematic biases or limitations inherent to the particular trial design and conduct. In contrast, positive results from two nonidentical trials may be more persuasive, as unrecognized flaws may be less likely to impact the outcomes of both trials. Furthermore, two nonidentical trials can provide additional information about a drug's effect. For example, one trial studying a new glucose-lowering drug in participants with type 2 diabetes receiving only diet and exercise therapy, and a second trial in participants with type 2 diabetes already on two or three oral antihyperglycemic agents, may provide evidence that is both persuasive and applicable to the broad population expected to take the drug if approved. Similarly, two trials in the same disease using different but related clinical endpoints could support effectiveness and provide broader information about the drug's effect (e.g., one trial showing symptom improvement and a second trial showing improved survival in a more severely ill population with the same condition).

Sponsors may opt to conduct more than one adequate and well-controlled clinical investigation based on the needs of their specific development programs, including operational and feasibility considerations. FDA divisions may also recommend more than one adequate and well-controlled trial in some settings. Examples of times when a second clinical trial may be appropriate include when a trial is not sufficiently representative of the broad population expected to use the drug (e.g., an intended indication that includes older or younger age groups than were included in the trial), is not sufficient to support a reliable safety and benefit-risk assessment, or has some other specific underlying limitation or deficiencies (e.g., does not address considerations discussed in section IV.A). However, in these circumstances, sponsors can propose alternative single adequate and well-controlled trial designs intended to address the limitations.

All relevant trials should be considered in evaluating a drug's effectiveness. If multiple adequate and well-controlled trials are conducted, the design, conduct, analysis, and results from all the trials will factor into the evaluation of the strength of evidence.

C. A New Population or a Different Dose, Regimen, Route of Administration, or Dosage Form, Based on the Known Effectiveness of an Approved Drug When Scientifically Justified and Legally Permissible

When scientifically justified and legally permissible, a sponsor can leverage the known effectiveness of an approved drug to demonstrate substantial evidence of effectiveness for a new use or condition without needing to conduct adequate and well-controlled clinical investigations. Ordinarily, this will be because other types of evidence provide a way to apply the known

effectiveness to a new related population or a different dose, regimen, route of administration, or dosage form. For example, the effectiveness of a drug for pediatric use can sometimes be based on the known effectiveness of the drug in adults, together with scientific evidence that justifies this approach to support approval for pediatric use.[36] In this case, the scientific evidence may include, for example, evidence supporting similarity in the disease course, drug pharmacology, and response to treatment between an adult population and a pediatric population.[37]

The effectiveness of a new dose, regimen, route of administration, or dosage form may be demonstrated by the trial(s) that used the original dose, regimen, route of administration, or dosage form, together with evidence that the new modification yields similar pharmacokinetic profiles or evidence that any differences in pharmacokinetics are not expected to translate to clinically relevant differences in effectiveness. In this case, although no new effectiveness or pharmacodynamic data may be needed, additional safety data may still be needed.

V. REGULATORY FLEXIBILITY

While the statutory standard of effectiveness applies to all drugs, given the many types of drugs and uses for them, FDA exercises flexibility in applying the standard in certain critical settings.[38] FDA's application of flexibility reflects the awareness that in certain critical settings a somewhat greater uncertainty about effectiveness may be warranted when balanced against the risk of rejecting or delaying the marketing of an effective therapy. There is long-standing support for such an approach; for example, FDA regulations at 21 CFR part 312, subpart E promulgated in 1988[39] call for FDA to exercise its broad scientific judgment in applying the evidentiary approval standards to drugs for life-threatening and severely debilitating diseases, especially where there is no satisfactory alternative therapy. This approach has been reinforced by FDA's interactions with patients and their caregivers in such circumstances, many of whom describe a willingness to accept less certainty about effectiveness in return for earlier access to medicines.

There is no single set of clinical considerations that lead to the application of flexibility, and there is no single definition of what constitutes a flexible approach for drug development and regulatory decision-making. This section provides examples of when and how flexibility may be applied. Sponsors should have early discussions with FDA about their intended approach to demonstrate substantial evidence of effectiveness in settings where flexibility may be appropriate.

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[36] Section 505B(a)(2)(B)(i) of the FD&C Act (21 U.S.C. 355c(a)(2)(B)(i)).

[37] See the ICH guidance for industry *E11A Pediatric Extrapolation* (December 2024).

[38] For example, FDA published proposed recommendations regarding the application of regulatory flexibility for individualized therapies that target specific genetic conditions with known biological causes, specifically genome editing and RNA-based therapies for diseases in a small number of patients. See the draft 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* (February 2026). When final, this guidance will represent the FDA's current thinking on this topic.

[39] 21 CFR part 312, subpart E; 21 CFR 314.105(c).

A. Clinical Circumstances Where Flexibility May Be Warranted

The clinical context is critical to informing the approach to establishing substantial evidence of effectiveness. Considerations include, for example, disease severity, unmet need, and disease rarity. Regarding disease severity, 21 CFR part 312, subpart E (21 CFR 312.81) defines *life-threatening* as "diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted," and "diseases or conditions with potentially fatal outcomes, where the end point of clinical trial analysis is survival." The same regulation defines *severely debilitating* as "diseases or conditions that cause major irreversible morbidity." The guidance for industry *Expedited Programs for Serious Conditions – Drugs and Biologics* (May 2014) describes an *unmet medical need* as "a condition whose treatment or diagnosis is not addressed adequately by available therapy." *Rare disease or condition* is defined, in part, in the FD&C Act as any disease or condition that "affects less than 200,000 persons in the United States."[40] Many rare diseases affect far fewer patients, and a large number of rare diseases are pediatric diseases or have childhood onset.

These clinical considerations should not be considered individually, but rather holistically, as more than one consideration will often be relevant. For example, many rare diseases are life-threatening and lack available therapy. In general, all relevant clinical considerations (e.g., disease severity, unmet need, and disease rarity) should inform the extent and types of flexibilities that may be appropriate. For example, certain flexibilities might be more acceptable for a rare disease that is life-threatening and lacks available therapies than another rare disease with less severe consequences with multiple therapeutic options already available. Both of these scenarios, however, present a very different clinical context than a common, nonserious disease with several available treatment options. However, in all scenarios, whether the disease is rare or common, fatal or less severe clinically, substantial evidence of effectiveness must be demonstrated.

B. How Flexibility May Be Applied

1. Trial Design and Analysis

When scientifically sound and clinically appropriate, FDA may exercise flexibility with respect to certain trial designs and analysis plans that may result in less certainty about effectiveness. Sometimes, departures from more typical designs may result in less certainty about effectiveness; the degree of uncertainty will be impacted by the assumptions inherent to the design choice and the extent to which those assumptions may be violated. For example, the extent to which an externally controlled trial meets the expectations outlined in section III.A (e.g., well-defined natural history, comparability of the external control and treatment groups) will impact certainty about effectiveness. Even when assumptions may not fully be met, it may

[40] Section 526(a)(2)(A) of the FD&C Act (21 U.S.C. 360bb(a)(2)(A)). In addition, section 526(a)(2)(B) of the FD&C Act also defines a rare disease or condition as any disease or condition that "affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug."

sometimes be possible to conclude that substantial evidence of effectiveness has been demonstrated despite residual uncertainty (e.g., when the observed effect size is so large that it is unlikely to be fully attributable to bias).

The degree of certainty about effectiveness can also be impacted by endpoint selection. Endpoints vary with respect to factors such as interpretability, ease of measurement, susceptibility to bias, and the extent to which they directly measure clinical benefit. A decision to accept a greater degree of uncertainty attributable to such factors with a proposed primary endpoint is an example of FDA exercising flexibility.

In certain clinical circumstances, some flexibility in success criteria for the primary statistical analysis may also be acceptable. For example, in a trial relying on null hypothesis significance testing, a significance level higher than the common one-sided 0.025 level may be acceptable in some cases. The success criteria should be prespecified, justified, and agreed upon with the Agency. The choice of success criteria should consider a variety of factors that impact the consequences of false positive and false negative conclusions, such as the factors described above (see section V.A) and the feasibility of different trial designs and sample sizes (e.g., the degree to which studies of different sizes and with different significance levels would be adequately powered to detect meaningful effect sizes).

Trials in rare diseases may have smaller sample sizes, resulting in a less precise characterization of effectiveness. In such situations, it is especially important to consider the advantages and disadvantages of various trial designs and to optimize the trial's potential to provide interpretable results. This can be facilitated by using trial design and analysis features such as randomization, blinding, appropriate endpoint selection, covariate adjustment,[41] and adequate trial duration.[42]

2. Sources and Strength of Confirmatory Evidence

When scientifically sound and clinically appropriate, FDA may exercise flexibility with respect to the sources and strength of confirmatory evidence that may be appropriate in combination with evidence from a single adequate and well-controlled trial.

For example, mechanistic evidence of the drug's treatment effect in a particular disease may be appropriate to use as confirmatory evidence. Mechanistic evidence might be generated with a clinical trial of a pharmacodynamic endpoint or with nonclinical studies. The pathophysiology of the disease should be well-understood, and the drug's mechanism of action should be both clearly understood and shown to directly target the major driver(s) of the disease pathophysiology. An example might be when the disease is caused by a single gene and/or enzyme defect, and the drug's mechanism of action corrects the enzymatic or genetic defect or its sequelae.

[41] See the guidance for industry *Adjusting for Covariates in Randomized Clinical Trials for Drugs and Biological Products* (May 2023).

[42] For further discussion, see the guidance for industry *Rare Diseases: Considerations for the Development of Drugs and Biological Products* (December 2023).

In certain circumstances, natural history data may also provide confirmatory evidence. For example, a single randomized controlled trial showing marked improvement in survival could be supported by data from separate sources (e.g., a natural history study or registry) that demonstrate a very limited median survival time without treatment. The natural history data would provide reassurance that the outcomes observed in the control group of the trial accurately reflect those that would have been expected in the absence of the intervention. Natural history data being used as confirmatory evidence should be distinct from any data used as a control for the single adequate and well-controlled trial. Leveraging natural history data may involve use of real-world data (RWD) sources. Whether an RWD source may be appropriate to provide confirmatory evidence depends on several factors, such as the reliability and relevance of the RWD source for its proposed use and, when relevant, the appropriateness of the study design and the use of appropriate prespecified statistical methods and analyses.[43]

Other sources of confirmatory evidence may be reasonable in certain settings, and multiple sources may be evaluated within a drug development program. Sponsors should submit and FDA will carefully consider all relevant information, including not only information that may support effectiveness but also information providing conflicting evidence. The evaluation of whether substantial evidence of effectiveness has been demonstrated will depend on the strength of the design, conduct, analysis, and results of the single adequate and well-controlled trial, the strength of the confirmatory evidence, and the clinical context.

VI. SAFETY CONSIDERATIONS

An FDA approval decision, among other things, requires a determination that a drug is safe for its intended use, which involves assessing whether the benefits of the drug outweigh its risks. Detailed considerations for the safety evaluation and benefit-risk assessment[44] are beyond the scope of this guidance. However, it is important to note that sponsor development programs should be planned to both demonstrate effectiveness and support an appropriate safety and benefit-risk assessment. In some cases, adequate and well-controlled trial(s) that are sufficient to demonstrate effectiveness may not include a sufficient number of participants or a sufficient treatment duration to conclude that the drug is safe for its intended use. A larger or longer trial or an additional trial may be needed to ensure a safety database of adequate size and duration to support an appropriate benefit-risk assessment and drug approval. Sponsors should consult relevant guidances that discuss general expectations for the extent of drug exposure to assess

[43] See the guidances for industry *Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products* (July 2024)*, Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products*, *Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products* (December 2023), and *Data Standards for Drug and Biological Product Submissions Containing Real-World Data* (December 2023). Also refer to FDA's Real-World Evidence web page, available at https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence.

[44] See the guidance for industry *Benefit-Risk Assessment for New Drug and Biological Products*.

586 safety, as well as additional factors that may impact the appropriate size of a safety database and
587 other aspects of development program planning for the evaluation of drug safety.[45]

[45] See the ICH guidance for industry *E1A The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions* (March 1995) and the guidance for industry *Premarketing Risk Assessment* (March 2005). There also may be relevant disease-specific guidances that discuss safety considerations. When there is an adequate safety database for approval, FDA may also require or request that additional safety information be obtained in the postmarketing setting through the conduct of studies as postmarketing requirements or commitments.