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

## Guidance for Industry

## *DRAFT GUIDANCE*

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**Clinical/Medical**

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# Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence Guidance for Industry[1]



## I. INTRODUCTION

This guidance (the Confirmatory Evidence guidance) complements the draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019) (the 2019 Effectiveness draft guidance)[2] and the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998) (the 1998 Effectiveness guidance). This guidance provides recommendations for sponsors to consider when planning a drug[3] development program.

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. BACKGROUND AND SCOPE

In 1962, Congress required for the first time that drugs be shown to be effective as well as safe. A drug's effectiveness must be established by *substantial evidence*, which is defined as

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

[2] When final, this guidance will represent the 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.

[3] For the purposes of this guidance, all references to *drugs* include both human drugs and biological products, unless otherwise specified.

> [E]vidence 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.[4]

FDA has interpreted this substantial evidence requirement as generally requiring two adequate and well-controlled clinical investigations, each convincing on its own, to establish effectiveness. Nevertheless, as noted in the 1998 Effectiveness guidance, FDA has also been flexible within the limits imposed by the statute where data on a particular drug were convincing. In 1997, Congress amended section 505(d) to confirm FDA's interpretation of the statutory requirements, making clear that FDA may consider data from one adequate and well-controlled clinical investigation and confirmatory evidence to constitute substantial evidence if FDA determines that such data are sufficient to establish effectiveness.[5] Specifically, Congress added to section 505(d) that

> If [FDA] determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, [FDA] may consider such data and evidence to constitute substantial evidence.

FDA issued the 1998 Effectiveness guidance in response to this legislative change. The 1998 guidance provides examples of the types of evidence that could be considered confirmatory evidence, with a specific focus on adequate and well-controlled trials of the test agent in related populations or indications, as well as a number of illustrations of a single adequate and well-controlled trial supported by convincing evidence of the drug's mechanism of action in treating a disease or condition.

Although FDA's evidentiary standard for effectiveness has not changed since 1998, drug development and science have continued to evolve, leading to changes in the nature of drug development programs submitted to the Agency. In 2019, the Agency concluded that more guidance was needed on the flexibility in the amount and type of evidence needed to meet the substantial evidence standard. The 2019 Effectiveness draft guidance discusses a number of approaches that can yield evidence that meets the statutory standard for substantial evidence, and in particular addresses the agency's consideration of various trial designs, trial endpoints, and statistical methodologies, reflecting the Agency's long-standing flexibility when considering the types of data and evidence that can meet the substantial evidence requirement.

Given the range of topics addressed by the 2019 Effectiveness draft guidance, its discussion of meeting the substantial evidence standard based on one adequate and well-controlled clinical

[4] Under section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. 262), licenses for biologics 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 of the PHS Act.

[5] The Food and Drug Administration Modernization Act of 1997 (FDAMA) (Pub. L. 105–115),

investigation plus confirmatory evidence was necessarily brief. This guidance supplements the discussion in the 2019 Effectiveness draft guidance by providing further detail on the use of data drawn from one or more sources (e.g., clinical data, mechanistic data, animal data) to substantiate the results of one adequate and well-controlled clinical investigation.

This guidance describes factors to consider when assessing whether a single adequate and well-controlled clinical investigation and confirmatory evidence are sufficient to demonstrate substantial evidence of effectiveness. It also provides examples of types of data that could be considered confirmatory evidence. This guidance also emphasizes the importance of early engagement with the Agency for sponsors that intend to establish substantial evidence of effectiveness with one adequate and well-controlled clinical investigation and confirmatory evidence.

This guidance does not discuss the development paradigm in which, under certain circumstances, a single multicenter trial can satisfy the legal requirement for substantial evidence of effectiveness; that scenario is discussed in the 2019 Effectiveness draft guidance. This guidance also does not discuss approval of a different dose, regimen, or dosage form based on a previous finding of effectiveness of an approved drug, or other regulatory considerations beyond the scope of the substantial evidence determination under section 505(d) of the Act. In addition, in some situations, a sponsor may intend to rely on data submitted in other applications to support a new drug application. This guidance does not address certain regulatory considerations that apply to reliance on certain types of information in 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 in a 505(b)(2) application).[6]

The finding of substantial evidence of effectiveness is necessary but not sufficient for FDA approval. An approval decision, among other things, also requires a determination that a drug is safe for its intended use.[7] As all drugs can have adverse effects, evaluating whether a drug is "*safe*" involves weighing whether the benefits of the drug outweigh its risks. In some cases, one adequate and well-controlled clinical investigation and confirmatory evidence may demonstrate effectiveness, but the clinical trial may not have enrolled a sufficient number of participants or have treated them for a sufficient duration to conclude that the drug is safe. A second clinical trial may be needed to ensure a safety database of adequate size and duration to support an appropriate benefit-risk assessment. Considerations for a safety evaluation, a benefit-risk analysis, and their impact on the acceptability of one trial with confirmatory evidence to support approval are beyond the scope of this guidance.

[6] For discussion of this topic, 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. 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. Note, also, that use of certain sources of information may not be permitted under certain regulatory pathways, but that discussion is beyond the scope of this guidance.

[7] Section 505(d) of the FD&C Act.

## II. GENERAL CONSIDERATIONS REGARDING CONFIRMATORY EVIDENCE AND THE DEMONSTRATION OF SUBSTANTIAL EVIDENCE OF EFFECTIVENESS

The substantial evidence of effectiveness standard in the FD&C Act (see section II) refers to both the quantity and quality of the evidence. As noted above, the number of trials required to demonstrate substantial evidence of effectiveness can vary across development programs. The 2019 Effectiveness draft guidance discusses, in part, the features of adequate and well-controlled clinical investigations,[8] with a focus on trial design, endpoints, and statistical considerations. A clinical investigation's particular set of features will result in a greater or lesser degree of certainty about effectiveness.

When one adequate and well-controlled clinical investigation and confirmatory evidence are considered together to assess effectiveness, the quality and quantity of confirmatory evidence are also important considerations. Confirmatory evidence should be evidence generated from quality data derived from an appropriate source (see section III).

The quantity (e.g., number of sources) of confirmatory evidence necessary to support effectiveness may vary across development programs. Importantly, the quantity of confirmatory evidence needed in a development program will be impacted by the features of, and results from, the single adequate and well-controlled clinical investigation that the confirmatory evidence is intended to substantiate. It may be possible for a highly persuasive adequate and well-controlled clinical investigation to be supported by a lesser quantity of confirmatory evidence, whereas a less-persuasive adequate and well-controlled clinical investigation may require a greater quantity of compelling confirmatory evidence to allow for a conclusion of substantial evidence of effectiveness.

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.[9] The results of a clinical investigation or confirmatory evidence can be called into question by conflicting evidence unless there is a sufficient scientific justification that may explain the disparate findings.

When evaluating whether to approach establishing substantial evidence of effectiveness with one adequate and well-controlled clinical investigation and confirmatory evidence, sponsors should consider the clinical context for the proposed therapy. Disease- or condition-specific considerations (e.g., unmet need, size of the patient population) may be relevant to whether such an approach is appropriate. Furthermore, although safety considerations are beyond the scope of this guidance, decision making about a drug development program should also take into account the data necessary to demonstrate that a drug is safe for the intended use.

[8] See 21 CFR 314.126(b) for additional information on the features of adequate and well-controlled investigations.

[9] See 21 CFR 314.50(d)(5)(iv).

Sponsors who plan to establish substantial evidence of effectiveness with a single adequate and well-controlled clinical investigation and confirmatory evidence should discuss their proposed approach with FDA early in development, such as at a pre-IND meeting and no later than when the sponsor is seeking feedback regarding the clinical investigation (e.g., at the end-of-phase 2 meeting; see section IV).[10] When meeting with FDA, sponsors should be prepared to provide a rationale for their chosen approach to development, along with descriptions of the planned single adequate and well-controlled clinical investigation and planned confirmatory evidence. The goal of such engagement is to allow the sponsor and Agency an opportunity to evaluate whether a development program consisting of a single adequate and well-controlled clinical investigation and confirmatory evidence could demonstrate substantial evidence of effectiveness. Ultimately, whether a single adequate and well-controlled clinical investigation and confirmatory evidence are sufficient to demonstrate substantial evidence of effectiveness will depend on the results generated by the development program.

## III. TYPES OF CONFIRMATORY EVIDENCE

This section provides examples of types of confirmatory evidence that can, in appropriate circumstances, be used to substantiate one adequate and well-controlled clinical investigation to demonstrate substantial evidence of effectiveness. This section is not intended to provide an exhaustive list. We note that some of these examples involve data that are frequently generated during a conventional drug development program, and that such data may or may not be appropriate as confirmatory evidence depending on the specific development program under consideration. Whether confirmatory evidence and the adequate and well-controlled clinical investigation provide substantial evidence of effectiveness is determined case by case, for each application, in the context of the application as a whole.

### A. Clinical Evidence from a Related Indication

Under certain circumstances, evidence of effectiveness of a drug from a clinical investigation for a particular indication can provide confirmatory evidence of effectiveness to support approval of the drug in a different but closely related indication.

A common example of this approach is the submission of a new drug application or a biologics license application for a new indication for an already approved therapy, where one adequate and well-controlled clinical investigation of the drug for the new indication is supported by the results from the clinical investigation or investigations that formed the basis of the previous approval (for a different but closely related indication). In another example, one adequate and well-controlled clinical investigation in each of two related, unapproved indications can serve as confirmatory evidence for the other indication, thereby supporting concurrent approval of the drug for both indications.

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 for a trial that studied

[10] See the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (December 2017). When final, this guidance will represent the FDA's current thinking on this topic.

the drug for a different indication, are the degree of similarity between the indications, 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 two diseases.

Examples of when clinical 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)

- A different but closely related disease, for example:

  - Infections at different anatomical sites caused by similar pathogens against which the drug is active (e.g., bone/joint infections and acute bacterial skin and skin structure infections)

  - Diseases with a common precursor targeted by the product (e.g., genital warts and cervical cancer both prevented by human papillomavirus vaccine through prevention of infection)

  - Diseases with similarities in their underlying pathophysiology (e.g., rheumatoid arthritis and psoriatic arthritis)

### B. Mechanistic or Pharmacodynamic Evidence

Under certain circumstances, strong mechanistic evidence of the drug's treatment effect in a particular disease may be appropriate to use as confirmatory evidence. In such cases, (1) the pathophysiology of the disease should be well understood and (2) the drug's mechanism of action should be both clearly understood and shown to directly target the major driver or drivers of the disease pathophysiology. When the drug's mechanism of action affects several pathophysiologic pathways and it is not clear which pathway is important to disease occurrence and/or progression, mechanistic data may not provide sufficient confirmatory evidence to support approval, and additional evidence from other sources may be needed. Similarly, when a disease has multiple causal pathways that lead directly to disease occurrence or progression and the drug only impacts one causal pathway, mechanistic data may not provide sufficient confirmatory evidence.

Mechanistic evidence is generally obtained from clinical testing using a relevant and well-understood pharmacodynamic endpoint[11] not accepted by itself as an endpoint to establish evidence of effectiveness. Mechanistic evidence can also be obtained from *in vitro* testing (e.g., if the disease is caused by a genetic defect that results in defective function of an anion transporter on epithelial cells, in vitro evidence in a relevant cell line and at relevant concentrations demonstrating that the drug directly augments transporter function). The quality and strength of mechanistic data exist on a spectrum, ranging from exploratory in nature to results that demonstrate clear evidence for a particular pathophysiological mechanism of disease and the drug's effect on the established mechanism.

Examples of when mechanistic data may be appropriate for use as confirmatory evidence include the following:

- 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. For example:
  - An enzyme replacement therapy that corrects the underlying enzymatic deficiency in a lysosomal storage disease at the affected target tissues or organs (e.g., laronidase in mucopolysaccharidosis type I)
  - A small-molecule drug that increases a metabolite, or decreases a precursor, in a disease caused by an enzymatic block in its biosynthetic pathway, resulting in absence or reduced levels of that metabolite (e.g., uridine replacement in hereditary orotic aciduria), and/or elevation of the precursor chemical
  - An antisense oligonucleotide directed at a specific gene variant or molecular genetic mechanism causing an inborn error of metabolism or genetic disease (e.g., overexpression of a gene leading to overexpression of an enzyme), where biochemical data in the target organ shows expected changes in gene expression (e.g., knockdown of the gene expression in the tissue and decreased enzyme activity)
  - Nonclinical data demonstrating concentration-dependent inhibition of cell proliferation or signaling correlating with inhibition of an oncogene-dependent pathway (e.g., single driver mutation) in a specific cancer type
- When the therapy is a chelating or binding agent, where there is a body of evidence describing the clinical consequences of excessive amounts of a substrate (e.g., iron,

[11] In some settings where the pathophysiology of a disease is not well understood, a pharmacodynamic biomarker might not elucidate a drug's mechanism of action but could still provide information about a clinical outcome. In an appropriate case, the results of a single adequate and well-controlled clinical investigation could be substantiated by the confirmatory evidence provided by the pharmacodynamic data. Demonstration of a well-characterized exposure-response relationship for the pharmacodynamic biomarker may be particularly persuasive as confirmatory evidence when such data suggest that the effect observed in a successful adequate and well controlled clinical investigation is more likely attributable to the pharmacological action of the drug than to chance.

potassium, phosphate), and in vitro or in vivo data convincingly demonstrate the ability of the drug to bind a meaningful percentage of the substrate

- When the therapy is an antimicrobial drug, proposed for use in combination with a novel inhibitor of a bacterial-resistance mechanism (e.g., beta-lactam antibacterial drug with a novel beta-lactamase inhibitor), and in vitro and animal data demonstrate increased activity of the combination compared with the antimicrobial alone against organisms resistant to the antimicrobial alone

### C. Evidence from a Relevant Animal Model

Animal data (e.g., proof-of-concept data, pharmacological studies, toxicology studies) are used in drug development for a number of purposes, including to help characterize a therapy's pharmacodynamic effects (which may be done either in healthy animals or in animal models of disease, as appropriate); provide evidence of efficacy in an animal model of disease, using an endpoint that is intended to reflect or translate to a similar outcome in humans with disease; or profile drug toxicity.[12] Typically, results of studies conducted in an animal model of disease are intended to support progressing a drug candidate forward from preclinical to clinical development, rather than to support a finding of substantial evidence. Infrequently, however, sponsors can use data from an established animal model of disease as confirmatory evidence of effectiveness; in such cases, sponsors should discuss in advance these planned nonclinical studies with the appropriate FDA review division.

Whether data from an established animal model of disease would be suitable as confirmatory evidence depends on several factors, including similarity of pathophysiology and manifestations of the disease in the animal model and in humans, elucidation of the drug's mechanism of action with evidence of similar pharmacology and pharmacodynamics in the animal model and humans with disease, and evidence that the results of efficacy studies conducted in the animal model reasonably support clinical benefits and outcomes in humans with disease (e.g., if the disease in humans leads to renal failure and the drug is intended to preserve renal function, showing that the animal model of disease also is characterized by renal failure and the drug reduces progression of renal failure when tested in the animal model). Although animal models are useful in the preclinical stages of drug development, only a few such models may accurately predict human responses quantitatively or even qualitatively. Only models that have proved to be translational (i.e., prior drugs with the same intended clinical effect have been shown to have this effect observed in the animal model, with similar exposure-response) are likely to be considered as confirmatory evidence.

Examples of when animal data may be appropriate for use as confirmatory evidence include the following:

[12] FDA supports the principles of the 3Rs (reduce/refine/replace) for animal use in testing when feasible. FDA encourages sponsors to consult with review divisions when considering a nonanimal testing method believed to be suitable, adequate, validated, and feasible. FDA will consider if the alternative method could be assessed for equivalency to an animal test method.

- When the drug is an antimicrobial agent, and there is a well-established model of infection for a relevant infectious disease, and use of the therapy in the animal model demonstrates antimicrobial activity

- When the product is a preventive vaccine, and there is a well-established model of infection for a relevant infectious disease, and use of the vaccine in the animal model demonstrates prevention of disease

Using animal model data as confirmatory evidence of effectiveness in the setting of one adequate and well-controlled clinical investigation is distinct from the approval pathway established in FDA regulations collectively known as the *animal rule*,[13] although some of the considerations that are relevant to approval under the animal rule (e.g., the need for a well-understood underlying pathophysiology, the predictiveness of the animal model, and the relatedness of the animal efficacy to the desired benefit in humans)[14] may also be relevant where results of studies conducted in an animal model are used as confirmatory evidence of effectiveness.

### D. Evidence from Other Members of the Same Pharmacological Class

In certain circumstances, FDA has accepted one adequate and well-controlled clinical investigation as the basis to demonstrate effectiveness, when the single trial is supported by confirmatory evidence of effectiveness from adequate and well-controlled trials of other drugs in the same pharmacological class approved for the same indication.[15] The ability to use information about drugs in a pharmacological class as confirmatory evidence generally depends on all of the following:

- The mechanism of action of the new drug, which should be the same as that of approved members of the class.

- The extent to which similar endpoints were measured across the class, and the homogeneity of each drug's effect on clinical outcomes. Relevant considerations generally include whether the new drug has similar effects on the same endpoints assessed for approved drugs, or whether the new drug demonstrates positive effects on some endpoints and no effect or adverse effects on others.

- The consistency and predictability of the measured effect among drug class members.

[13] 21 CFR part 314, subpart I (drugs) and 21 CFR part 601, subpart H (biological products). The animal rule only applies when it is not ethical or feasible to conduct clinical studies. In such situations FDA can allow the use of adequate and well-controlled efficacy studies in appropriate animal models to generate evidence to establish effectiveness of products intended to treat or prevent serious or life-threatening conditions caused by exposure to lethal or permanently disabling toxic biological, chemical, radiological, or nuclear substances.

[14] See 21 CFR 314.610(a).

[15] See footnote 6.

- The number of drugs approved in the class. Although it is not possible to assign a threshold number, the greater the number of approved drugs in a class that demonstrate the same general effects, the greater the confidence is likely to be that these effects are related to a common pharmacological effect.

### E. Natural History Evidence

In certain circumstances, natural history data can provide confirmatory evidence to substantiate the results of a single adequate and well-controlled investigation. Such an approach can be useful when there is uncertainty about whether the outcomes observed in the control group 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 clinical investigation.

Examples of when natural history data may be appropriate for use as confirmatory evidence include the following:

- A novel drug to treat patients with an acquired blood enzyme deficiency, where patients had high levels of the abnormal blood protein at baseline with deficient oxygen-carrying capacity. In the double-blind, placebo-controlled crossover design clinical trial, each participant served as his or her own control, with demonstration of nonmeasurable abnormal blood protein levels and improvement in oxygenation after drug administration but not after administration of placebo, and complete resolution of this disorder. The evidence from the one adequate and well-controlled clinical investigation could be supported by confirmatory evidence, from natural history data, which demonstrates failure of this disorder to spontaneously resolve with subsequent high morbidity and mortality.

- A drug for a progressive disease, for which the adequate and well-controlled clinical investigation demonstrates stability of a clinically important outcome in the experimental group compared with deterioration in the control group, and for which natural history data are available to confirm the amount of deterioration in the control group is an expected outcome for the period of observation.

### F. Real-World Data/Evidence

Pursuant to section 3022 of the 21st Century Cures Act[16] FDA developed a program to evaluate the potential use of real-world evidence to help support the approval of a new indication for a drug already approved under section 505(c) of the FD&C Act or to help support or satisfy post-approval study requirements.[17]

[16] Public Law 114–255, signed December 13, 2016.

[17] This real-world evidence program also covers biological products licensed under the Public Health Service Act. See Framework for FDA's Real-World Evidence Program, available at https://www.fda.gov/media/120060/download.

For the purposes of this guidance, FDA defines real world data (RWD) and real-world evidence (RWE)[18] as follows:

- RWD are data relating to patient health status or the delivery of health care routinely collected from a variety of sources (e.g., electronic health records, medical claims data, registries).

- RWE is the clinical evidence about the usage and potential benefits or risks of a drug derived from analysis of real-world data.

As noted above, confirmatory evidence can come from one or a variety of sources, including RWD sources. Whether an RWD source may be appropriate to develop RWE that serves as confirmatory evidence depends on several factors, including but not limited to the reliability and relevance of the RWD source and, when relevant, the quality of the study design and the use of appropriate prespecified statistical methods and analyses.[19] FDA recommends that sponsors discuss with the relevant review divisions any plans to use RWE as confirmatory evidence in a drug development program.

### G. Evidence from Expanded Access Use of an Investigational Drug

Expanded access generally refers to the use of an investigational drug when the primary purpose is to diagnose, monitor, or treat a patient's or group of patients' disease or condition rather than to obtain the kind of information about the drug that is generally derived from clinical trials.[20] It may also refer to use of an approved drug where availability is limited by a risk evaluation and mitigation strategy (REMS) for diagnostic, monitoring, or treatment purposes, by patients who cannot obtain the drug under the REMS.[21] Expanded access may be permitted where the patient or patients have a serious or immediately life-threatening diseases or conditions where there is no comparable or satisfactory alternative therapy available; where the potential patient benefit justifies the potential risks of treatment; and where the requested use will not interfere with the

[18] See the draft guidance for industry *Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products* (September 2021). When final, this guidance will represent the FDA's current thinking on this topic.

[19] See the draft guidances for industry *Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products*, *Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products* (December 2021), *Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products* (November 2021), and *Data Standards for Drug and Biological Product Submissions Containing Real-World Data* (October 2021). When final, these guidances will represent the FDA's current thinking on these topics. 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.

[20] 21 CFR 312.300(a); see also the guidance for industry *Expanded Access to Investigational Drugs for Treatment Use: Questions and Answers* (June 2016).

[21] Id.

initiation, conduct, or completion of clinical investigations that could support marketing approval of the expanded access use or otherwise compromise the potential development of the therapy for the expanded access.[22] Under FDA regulations, expanded access may be authorized if the relevant criteria are met for an individual patient, under either emergency or nonemergency conditions, or for a group of patients.[23]

Although the purpose of expanded access is not primarily for research, if the patient outcome information collected under expanded access use of the drug is of sufficient quantity and quality to be highly persuasive, the information may be considered for use as confirmatory evidence. Typically, however, only limited and inconsistent information is available from expanded access (e.g., source documents are often lacking, diagnostic criteria and stage of disease may vary, monitoring and outcome assessments vary across patients, among other limitations), and such information provides an incomplete picture of the course of events, which may make the information unfit for use as confirmatory evidence.

The following scenario is an example of how patient outcome information collected under expanded access could be used as confirmatory evidence:

- A new drug application for an antidote to treat overdose of a chemotherapy drug, where the application included patient outcome information from a large number of single patient emergency investigational new drug applications for which the sponsor collected detailed medical records, and the documented clinical results were markedly improved compared with the expected serious outcome in the absence of treatment. Such information could then potentially serve as confirmatory evidence supporting the results of one adequate and well-controlled clinical investigation.

## IV. PROCESS CONSIDERATIONS

As discussed above, FDA recommends that sponsors discuss early with the review divisions any plans to use one adequate and well-controlled clinical investigation and confirmatory evidence to establish substantial evidence of effectiveness. During these discussions, sponsors should do the following:

- Provide a strong scientific rationale to support the use of a single clinical investigation and confirmatory evidence for their specific drug development program, taking into account the considerations outlined in section III of this document.

- Describe the anticipated design of one adequate and well-controlled clinical investigation that the confirmatory evidence is intended to support.

[22] See 21 CFR 312.305(a).

[23] See 21 CFR 312.310; 312.315, and 312.320.

- Discuss the confirmatory evidence they intend to use to demonstrate, in conjunction with one adequate and well-controlled clinical investigation, substantial evidence of effectiveness. Sponsors should describe the type (i.e., data source) and quantity of confirmatory evidence that will be included in their application.

Sponsors should continue to meet with the Agency throughout product development, particularly if changes to the clinical investigation or confirmatory evidence are contemplated.