Rare Diseases: Considerations for the Development of Drugs and Biological Products

Guidance for Industry

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)

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Rare Diseases: Considerations for the Development of Drugs and Biological Products Guidance for Industry[1]

I. INTRODUCTION

The purpose of this guidance is to assist sponsors of drugs[2] for the treatment of rare diseases in conducting efficient and successful drug development programs. The statutory requirements for marketing approval for drugs to treat rare and common diseases are the same and issues discussed in this guidance are encountered in other drug development programs. These issues are frequently more difficult to address in the context of a rare disease for which there is often limited medical and scientific knowledge, poorly understood natural history data, sample size constraints, and lack of drug development experience.

This guidance does not contain discussion of the general issues of statistical analysis. Those topics are addressed in other documents, including ICH guidances for industry *E9 Statistical Principles for Clinical Trials*[3] (September 1998) and *E10 Choice of Control Group and Related*

[1] This guidance has been prepared by the Office of New Drugs and the Office of Translational Sciences 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] The term *drug,* as used in this guidance, refers to both human drugs and biological products unless otherwise specified.

[3] *Clinical trial* has the same meaning as the term *clinical investigation* as the latter is defined in FDA regulations (see 21 CFR 312.3(b)).

Issues in Clinical Trials (May 2001), respectively.[4] Additional FDA guidances cover other specific topics that may be of specialized interest.[5,6,7,8]

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

Section 526(a)(2)(A) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) defines a rare disease or condition, in part, as a disease or condition that "affects less than 200,000 persons in the United States."[9] Most rare diseases, however, affect far fewer people. The sponsor of an orphan drug (a drug intended for use in a rare disease or condition[10]) may be eligible for orphan-drug designation and certain financial incentives intended to help make developing drugs for small numbers of patients financially viable;[11] however, the Orphan Drug Act does not create a statutory standard for the approval of orphan drugs that is different from the standard for approval of drugs for common diseases or conditions.

[4] 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.

[5] See the ICH guidance for industry *E8(R1) General Considerations for Clinical Studies* (April 2022).

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

[7] 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. 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. Also 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).

[8] See the guidance for industry *E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials* (May 2021).

[9] 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."

[10] See 21 CFR 316.3(b)(10).

[11] Incentives associated with orphan-drug designation include a tax credit for 25 percent of qualified clinical trial costs, exemption from fees under the Prescription Drug User Fee Act, and potential eligibility for a 7-year period of market exclusivity. See Public Law 97-414 (1983), as amended.

Approval of any drug — for either a rare disease or a common disease or condition — must be based on substantial evidence of the drug's effectiveness for its intended use and sufficient information to conclude that the drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling.[12] Sponsors should demonstrate evidence of effectiveness in an identified population from adequate and well-controlled[13] clinical investigations.[14] FDA regulations provide flexibility in how the regulatory standard may be met. FDA "exercise[s] its scientific judgment" in determining the kind and quantity of data a sponsor is required to provide for individual drug development programs.[15] This flexibility extends from the early stages of development to the design of adequate and well-controlled clinical investigations required to demonstrate effectiveness to support marketing approval and to establish safety data needed for the intended use.

Many rare diseases are serious conditions with no approved treatments, leaving substantial unmet medical need for patients. FDA recognizes that rare diseases are highly diverse with varying prevalence, rates of progression, and degrees of heterogeneity that can affect both clinical manifestations and disease courses even within a condition. Further complexity is added depending on what is known about a disease's natural history and pathophysiology. As such, no one program can be designed exactly like another. FDA is committed to helping sponsors create successful drug development programs that address the particular challenges posed by each disease and encourages sponsors to engage early with the Agency to discuss their drug development program.

III. CONSIDERATIONS FOR NATURAL HISTORY STUDIES

All drug development programs benefit from a firm scientific foundation, including an understanding of disease natural history. The natural history of rare diseases is often poorly understood, and the need for prospectively designed, protocol-driven natural history studies initiated in the earliest drug development planning stages cannot be overemphasized. Although FDA does not require natural history studies, we advise sponsors to evaluate early the depth and quality of existing natural history knowledge to determine whether it is sufficient to inform their drug development programs.

For details about natural history studies, refer to the draft guidance for industry *Rare Diseases: Natural History Studies for Drug Development* (March 2019).[16]

[12] See section 505(d) of the FD&C Act (21 U.S.C. 355(d)).

[13] See 21 CFR 314.126.

[14] See 21 CFR 314.126.

[15] 21 CFR 314.105(c).

[16] When final, this guidance will represent the FDA's current thinking on this topic.

IV. NONCLINICAL STUDIES

Nonclinical studies are a mandated part of drug development.[17] The goal of the nonclinical program, which consists of in vitro and/or in vivo studies, is to provide evidence that the drug is "reasonably safe to conduct the proposed clinical investigations."[18] Nonclinical studies can also contribute to a better understanding of the drug's mechanism of action, metabolism, pharmacokinetics, pharmacodynamics, and possible efficacy. The data generated from nonclinical studies are important to the design of early-phase clinical investigations, particularly for selecting the starting clinical dose, dose escalation plan, dosing regimen, and route of administration. The nonclinical data may help guide the selection of patient eligibility criteria and will often determine important safety monitoring procedures based on the observed toxicological profile.

Internationally accepted guidelines discuss the general design of nonclinical safety studies and the timing of such studies relative to the conduct of a clinical development program.[19] Factors that FDA evaluates when determining areas of nonclinical flexibility include the pharmacological and chemical characteristics of the drug, the design and objectives of the proposed clinical investigations, the severity of the targeted disease (including the rate of progression to death or irreversible morbidity), adequacy of other available therapies, and the anticipated risks to humans based on the accumulated nonclinical toxicology and human data. When determining the relevance of existing data, a sponsor can consider factors such as drug product constituents, dosage form, route of administration, dose levels, and dosing regimen plan.

The sponsor should design the pivotal toxicology studies considering the biology of the disease, expected pharmacology of the drug, existing proof-of-concept (POC) data, proposed population to be studied (e.g., adult versus pediatric), and proposed clinical investigation design(s) for the clinical indication sought. Generally, healthy animals are the test system used in traditional toxicology testing and, in most circumstances, would be the test system used to support initiation of clinical investigations.[20] When an animal model of the disease is available, pharmacology and safety studies may contribute to understanding the actions of the drug on disease pathophysiology, inform safety in the context of that disease, and guide plans for measuring biological effects in patients. Combined POC and safety studies in animal models of human

[17] See 21 CFR 312.23(a)(8).

[18] 21 CFR 312.23(a)(8).

[19] See the ICH guidances for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* (January 2010) (ICH M3(R2)); *S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* (June 2011) (ICH S6(R1)); and *S9 Nonclinical Evaluation for Anticancer Pharmaceuticals* (March 2010) (ICH S9).

[20] We support the principles of the 3Rs (replace/reduce/refine) 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.

disease have been used in limited situations such as enzyme replacement therapy. Toxicology testing in an animal model of disease may contribute to the nonclinical support for clinical investigations but usually will not substitute for toxicology testing in healthy animals. However, safety evaluation in an animal model may be particularly valuable when drug toxicity is predicted to be more severe in the presence of disease pathophysiology.

It can also be appropriate to conduct the pivotal toxicology studies in juvenile animals when the indicated population is pediatric and/or the weight of evidence suggests a cause for concern for adverse developmental effects not otherwise evaluated by studies conducted to assess developmental and reproductive toxicity, or the data from adult animals (and adult humans, if appropriate) are inadequate.[21]

When clinical investigations are to be conducted in pediatric participants, POC data are required to establish a prospect of direct benefit to the pediatric population.[22] Robust animal model results may support the possibility of clinical benefit and the potential for a favorable benefit-risk assessment to support testing in children. However, for many rare diseases, an animal disease model may not exist or may not exhibit some of the clinically important manifestations of the disease. Sponsors should thoroughly understand the biological relevance and limitations of the animal model of disease if it is used in nonclinical studies. Data from relevant ex vivo or in vitro models, such as tissue explants or cell cultures from participant-derived samples, can also be used to support the POC in some instances (e.g., correction of an mRNA or protein expression or subcellular trafficking defect that is known to have a causal relationship to the disease).

FDA has determined that it is appropriate to exercise the broadest flexibility in applying the statutory standards, while preserving appropriate standards of safety and effectiveness, for products that are being developed to treat severely debilitating or life-threatening (SDLT) rare diseases.[23] For products being developed for SDLT rare disease indications, clinical investigations can often proceed with modifications to the typical nonclinical development programs described in guidance.[24] The degree of flexibility afforded to such programs may depend on a variety of factors, such as the adequacy of current treatment options, the mechanism of the drug, the safety findings from the available data, and the expected rate of progression to mortality or irreversible morbidity.

For SDLT rare disease indications, certain types of nonclinical data — primary pharmacology (including POC data); secondary pharmacology; safety pharmacology; in vitro absorption, distribution, metabolism, and excretion; and genetic toxicology data — is generally expected at the time of investigational new drug application (IND) submission, as appropriate, as outlined in

[21] See the ICH guidance for industry *S11 Nonclinical Safety Testing in Support of Development of Pediatric Pharmaceuticals* (May 2021).

[22] See 21 CFR 50.52, 50.53, and 50.55(c)(2).

[23] See 21 CFR 312, subpart E.

[24] See ICH M3(R2), ICH S6(R1), and ICH S9.

relevant regulations and guidance.[25] The IND application should also include results from good laboratory practice–compliant general toxicology studies of sufficient duration to support the proposed first-in-human clinical protocol.[26] The in vivo safety pharmacology assessments can generally be integrated into the general toxicology studies.

Modifications to the typical nonclinical development paradigm may be appropriate for SDLT rare disease indications in the following areas:

- Repeat-Dose General Toxicology Study Duration and Timing of Submission:

  - If the clinical investigation entry criteria define a phenotype that is anticipated to progress rapidly to mortality within approximately 1 year (i.e., similar prognosis as for advanced cancer), 1-month general toxicology studies will be adequate to evaluate support for early clinical development. The study reports from the completed subchronic general toxicology studies (typically of 3 months' duration) should be submitted before initiating pivotal clinical investigations (those intended to provide substantial evidence of clinical effectiveness) and would generally be adequate to support marketing.

  - If the clinical investigation entry criteria define a phenotype that would be expected to have a slower rate of progression to death or is characterized by major debilitating irreversible morbidity, then the 3-month general toxicology studies should be submitted to support clinical investigations of greater than 1 month's duration. Chronic toxicity studies, when warranted (see ICH M3(R2) or ICH S6(R1) as appropriate), should be ongoing at the time of submission of clinical investigation protocols of more than 3 months' duration. Study reports from the chronic toxicity studies can generally be submitted with the marketing application but should be submitted earlier if warranted. In cases where the shorter duration studies identify safety signals needing further characterization, the chronic toxicity studies should be completed before initiating the pivotal clinical investigation(s).

- Species Selection:

  - Sponsors should conduct nonclinical evaluations in pharmacologically relevant species. It may be appropriate to conduct the general toxicology studies in a single species, for example, if there is only one relevant species and the potential for off-target toxicity is low. In some cases, initiation of clinical investigations can be supported by POC studies of appropriate duration in animal disease models, with incorporation of adequate toxicological assessments into the POC study. For such modified POC studies, FDA encourages sponsors to discuss the adequacy of the study

[25] See 21 CFR 312.23. See also ICH M3(R2), ICH S6(R1), and ICH S9. Additionally, see the ICH guidances for industry *S7A Safety Pharmacology Studies for Human Pharmaceuticals* (July 2001), *S7B Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals* (October 2005), and *E14 and S7B Clinical and Nonclinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential — Questions and Answers* (August 2022).

[26] See 21 CFR 312.23(a)(8) and ICH M3(R2), ICH S6(R1), and ICH S9.

197 design (e.g., number of animals used and plans for tissue collection and evaluation,
198 good laboratory practice status) with the review division before initiating the study.
199
200 • Developmental and Reproductive Toxicity Assessment:
201
202 – An assessment of toxicity to embryofetal development can generally be submitted
203 with the marketing application;[27] however, it may be appropriate to defer submission
204 to after approval, depending on factors such as the indication and patient population.
205 In some instances, embryofetal developmental data may be requested earlier if there
206 is a cause for concern that needs to be better characterized. The need for fertility and
207 prenatal and postnatal development studies should be determined based on the patient
208 population and existing data concerning identified hazards to these endpoints. If these
209 studies are needed, the data would generally be submitted with the marketing
210 application or in the postmarket period, as appropriate.
211
212 • Carcinogenicity Assessment:
213
214 – If the conduct of carcinogenicity studies is warranted, these data should generally be
215 submitted with the marketing application. In certain circumstances, submission of
216 these data may be deferred to after approval. The timing of carcinogenicity studies
217 should be discussed with the review division as early as possible in the drug
218 development program.[28]
219
220 The suitability of any or all of the above flexibilities to any given development program needs to
221 be determined on a case-by-case basis. Therefore, FDA strongly encourages the sponsor to
222 discuss the proposed approach with the review division to obtain concurrence with the sponsor's
223 proposed nonclinical development program.[29]
224
225

[27] This is predicated on an expectation that effective pregnancy prevention measures will be employed by persons of childbearing potential enrolled in the clinical trials. See ICH M3(R2).

[28] See ICH S6(R1), and the ICH guidances for industry *S1A The Need for Long-term Rodent Carcinogenicity Studies of Pharmaceuticals* (March 1996) and *S1B(R1) Addendum to S1B Testing for Carcinogenicity of Pharmaceuticals* (November 2022).

[29] For recommendations on the substance and scope of nonclinical information needed to support clinical trials for cell therapy and gene therapy products, see the guidance for industry *Preclinical Assessment of Investigational Cellular and Gene Therapy Products* (November 2013).

V. CONSIDERATIONS IN CLINICAL DEVELOPMENT, EFFECTIVENESS, AND SAFETY

A. Clinical Pharmacology Considerations, Dose Selection, and Use of Biomarkers

The following should be considered about clinical pharmacology, dose selection, and use of biomarkers in rare disease drug development.

1. Clinical Pharmacology Considerations and Dose Selection

FDA expects that routine clinical pharmacology assessments typically undertaken during drug development will be performed in rare disease drug development programs.[30] The need for specific clinical pharmacology assessments may depend on factors such as what is known about the drug's disposition, drug interaction potential with any concomitant medications, comorbidities, the anticipated safety profile of the drug, and the potential impacts of organ impairment on a drug's pharmacokinetics.

In general, sponsors should evaluate the effects of more than one dosage on response using pharmacodynamic or other sensitive clinical measures of efficacy and safety to inform dosing. Use of more than one dosage provides a range of exposures that can be used to determine which dosage should be carried forward into registrational clinical investigations and which dosage is appropriate for the general population upon approval. Biospecimens for analysis of pharmacokinetics and/or pharmacodynamics should be obtained from all clinical investigation participants to aid in evaluation of exposure-response relationships and selection of the most appropriate dosage. Sponsors developing drugs for rare diseases should provide a comprehensive plan for clinical pharmacology assessments to FDA early in drug development and discuss the plan with the review division. Further information on dose selection is under subsection E., Additional Considerations Related to Clinical Development for Rare Disease Drugs.

2. Identification and Use of Biomarkers

Sponsors are encouraged to evaluate biomarkers that are relevant to the disease process and drug response throughout the course of drug development for rare diseases. When appropriate and feasible, sponsors should develop a plan for obtaining specimens from clinical investigation participants to evaluate the effects of the drug in relevant tissues. When biomarkers are used to support critical decisions, such as for patient monitoring, dose selection, or supporting efficacy

[30] See the guidances for industry *Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling* (May 2003), *Population Pharmacokinetics* (February 2022), *In Vitro Drug Interaction Studies – Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* (January 2020), *Clinical Drug Interaction Studies – Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* (January 2020). See also the draft guidance for industry *Pharmacokinetics in Patients with Impaired Renal Function - Study Design, Data Analysis, and Impact on Dosing* (September 2020). When final, this guidance will represent the FDA's current thinking on this topic.

and safety, adequate information should be provided to support the biomarker and validation of the assay method.[31] Early consultation with the appropriate review division is encouraged.

The following should also be considered for use of biomarkers in rare disease drug development:

- Identifying new biomarkers or modifying the use of existing biomarkers that may indicate effects on different steps in the pathophysiologic processes.
  - Predictive biomarkers may have critical roles in POC and dose-selection clinical investigations or in identification of characteristics of patients with greater potential to respond to therapy. Biomarkers that promptly indicate drug response might be used in a patient-specific manner to individualize the dosage or regimen.
- Identifying early biomarkers of disease or effects of interventions and biomarkers that could be used in adaptive and enrichment designs for greater efficiency.[32]
  - For example, values of a laboratory measurement expected to be sensitive to a drug's effect could be used to screen potential responders for inclusion in efficacy clinical investigations. Sponsors may also be able to identify clinical or genomic characteristics that predict response using these biomarkers.

The analytical validity of the assay(s) used for biomarker quantitation should be evaluated before the phase 3 clinical investigation.[33] In addition, standardized methods for sample collection, storage, shipment, and preparation should be used.

The guidance for industry and FDA staff *Qualification Process for Drug Development Tools* (November 2020) includes important information about the features of biomarkers used as endpoints.[34] For information about biomarker development within a specific drug development program, the sponsor should discuss with the appropriate review division.[35]

[31] See the draft guidance for industry and FDA staff *Biomarker Qualification: Evidentiary Framework* (December 2018). When final, this guidance will represent the FDA's current thinking on this topic.

[32] See the guidances for industry *Enrichment Strategies for Clinical Trials to Support Determination of Effectiveness of Human Drugs and Biological Products* (March 2019) and *Adaptive Designs for Clinical Trials of Drugs and Biologics*.

[33] See the guidance for industry *Bioanalytical Method Validation* (May 2018).

[34] There is no statutory requirement that biomarkers be qualified through this process.

[35] See the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (September 2023). When final, this guidance will represent the FDA's current thinking on this topic.

B. Clinical Investigation Design

In rare disease drug development, given the limited number of patients, it is crucial to optimize all aspects of clinical investigation design and standardize the collection and management of data to ensure quality and interpretability. In general, increased measurement variability and inconsistency reduce data interpretability and confidence in the results. Standardized operating procedures, quality assurance, and quality control are essential. This is especially important when the clinical investigation is being conducted at multiple sites.

The purpose of conducting clinical investigations of a drug product is to distinguish the effect of a drug on the target condition from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation.[36] Adequate and well-controlled clinical investigations provide the primary basis for determining whether there is substantial evidence to support the claims of effectiveness, and sponsors should discuss with FDA their anticipated approach to demonstrating substantial evidence of effectiveness early in the development process.[37] FDA's regulation at 21 CFR 314.126(b) describes characteristics of an adequate and well-controlled clinical investigation.[38]

Recommendations for the design of clinical investigations below reflect best practices for conducting rare disease clinical studies designed to demonstrate whether a drug is effective in a patient population. However, in certain rare disease development programs, such as cell and gene therapies, there may be situations where it would be reasonable to explore flexibility in clinical investigation design.[39] Important factors would include if there is a well-defined, predictable natural history and if the therapeutic product has a large treatment effect on an objective and reliably measured biomarker or clinical endpoint. In these situations, flexibility in design should be considered on a case-by-case basis in discussion with the review division.

Considerations that are particularly relevant to rare disease drug development are addressed below.

1. Controls

A critical element of an adequate and well-controlled study is the use of an appropriate control to enable reliable and unbiased, to the degree possible, efficacy assessments. Typically, use of a randomized concurrent control group (e.g., placebo, no treatment, active treatment) is recommended to distinguish changes occurring because of the drug from those changes occurring because of other factors, such as natural disease progression.

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[36] See 21 CFR 314.126(a).

[37] See section 505(d) of the FD&C Act (21 U.S.C. 355(d)); 21 CFR 314.126(a).

[38] See also the draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019). When final, this guidance will represent the FDA's current thinking on this topic.

[39] See the guidance for industry *Human Gene Therapy for Rare Diseases* (January 2020).

For serious rare diseases with unmet medical need, interest is frequently expressed in using an external control. In clinical investigations with external controls, outcomes in participants receiving the test treatment according to a protocol are compared with outcomes in a group of people external to the clinical investigation who had not received the same treatment.[40] However, the lack of blinding and inability to eliminate systematic differences between treatment groups, given the nonrandomized nature of the comparison, are limitations to the use of an external control group. For example, in the case of a historical external control, there may be systematic differences between the nonconcurrent treatment groups attributable to changes in standard of care or diagnostic approaches over time.

Given the limitations, external control designs are usually reserved for specific circumstances, such as clinical investigations where the drug effect can be demonstrated in diseases with well-understood and characterized natural history, high and predictable mortality or progressive and predictable morbidity, and clinical investigations in which the drug effect is large and self-evident.[41,42] The suitability of an externally controlled clinical investigation design warrants a case-by-case assessment, and early discussion with the relevant review division is recommended.

2. Randomization and Blinding

Randomization in combination with blinding is a powerful clinical investigation design feature to mitigate bias as it aims to balance both known and unknown factors that may affect the outcome. Randomized, double-blind, controlled clinical investigations are an efficient and effective way to generate data on clinically meaningful outcomes to demonstrate substantial evidence of effectiveness.[43] Thus, randomized, double-blind, controlled clinical investigations are generally the preferred approach.

Randomization of all enrolled clinical investigation participants, including those in the earliest phases of clinical development, helps ensure that each participant's contribution is interpretable, avoiding potentially misleading findings from open-label, single-arm, externally controlled clinical investigations. Stratification of randomization by important prognostic factors such as age or disease severity may be considered to improve comparability of treatment groups. FDA also recommends that sponsors consider adjustment for prognostic factors as covariates in statistical analyses to improve precision and power.[44]

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[40] See the draft guidance for industry *Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products*.

[41] See the draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products*.

[42] See the draft guidance for industry *Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products.*

[43] See ICH E9.

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

Sponsors should explore and address concerns about clinical investigation design (such as control arms and randomization) with patients, caregivers, and clinical investigators early in planning stages to avoid undermining clinical investigation recruitment and retention. Sponsors can sometimes address patient and family concerns by using modified clinical investigation designs, when appropriate, to demonstrate effectiveness and identify important safety signals. These designs retain the advantages of placebo-controlled clinical investigations and include features that minimize placebo exposure and enhance access to experimental therapies (e.g., dose response, delayed start, randomized withdrawal, crossover, adaptive designs with interim analysis, unequal randomization ratio).[45]

3. Innovative Designs

It is important that plans to use innovative clinical investigation designs be discussed in advance with the review division, ideally at the pre-investigational new drug application (pre-IND) meeting.[46] Examples of innovative or nontraditional approaches in rare diseases include Bayesian methods, n-of-1 clinical investigations, randomized delayed-start designs, crossover designs, and master protocols (where a common placebo arm is shared among different drug arms).[47]

For example, sponsors may be able to use Bayesian methods to maximize the use of information gleaned from early-phase studies or natural history studies. Bayesian methods also may inform pediatric clinical investigations through incorporation of adult clinical data.

The design of clinical investigations may allow early evidence to be used later in a clinical investigation, which may be especially helpful when there are limited numbers of participants to study, as is the case in rare diseases.[48] If an adaptive clinical investigation design is under consideration, a detailed statistical analysis plan including the key features of the clinical investigation design and preplanned analyses (including interim analyses) should be discussed with the review division before clinical investigation initiation.

C. Evidence of Effectiveness and Efficacy Endpoints

The overall goals of drug development programs are to demonstrate the effectiveness of a drug in treating or preventing a disease or condition, to assess the magnitude and frequency of that effect, and to assess the risks of the drug, thereby enabling a benefit-risk assessment and appropriate labeling.

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[45] See the guidance for industry *Adaptive Designs for Clinical Trials of Drugs and Biologics*.

[46] See the guidance for industry *Interacting with the FDA on Complex Innovative Trial Designs for Drugs and Biological Products* (December 2020).

[47] See the guidance for industry *Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics* (March 2022).

[48] See the guidance for industry *Adaptive Designs for Clinical Trials of Drugs and Biologics*.

One of the statutory requirements for drug marketing approval is substantial evidence that the drug will have its claimed effect.[49] This requirement is the same for all drugs regardless of whether they are for common or rare diseases. Adequate and well-controlled investigations of a drug are able to "distinguish the effect of a drug from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation."[50]

In addition to clinical investigation design considerations discussed above, the selection of appropriate endpoints is critical for a clinical investigation. An endpoint is a precisely defined variable intended to reflect an outcome of interest that is statistically analyzed to address a particular research question.[51] A precise definition of an endpoint typically specifies the type of assessments made, the timing of those assessments, the assessments used, and possibly other details, as applicable, such as how multiple assessments within an individual are to be combined. For many rare diseases, well-characterized efficacy endpoints appropriate for the disease are not available. The frequency of assessments and patients' (and caregivers') involvement in the selection, development, or modification of existing clinical outcome assessment measures and available instruments can improve the chances of success for the development program.[52]

Endpoint selection for a clinical investigation involves understanding the following:

- The range and course of clinical manifestations associated with the disease. Sponsors can often obtain this knowledge, along with possible differences among patient subtypes, from a natural history study of the disease.[53]

- The clinical characteristics of the specific target population, which may be a subset of the total population with a disease.

- The aspects of the disease that are meaningful to the patient and caregivers and that could be assessed to evaluate the drug's effectiveness at each of the different stages of disease and levels of disease severity.[54]

[49] See section 505(d) of the FD&C Act (21 U.S.C. 355(d)). For a biological product to be licensed under section 351 of the Public Health Service Act, a sponsor must demonstrate, among other things, that its product is safe, pure, and potent. Potency has long been interpreted to include effectiveness (21 CFR 600.3(s)).

[50] See 21 CFR 314.126(a).

[51] See the FDA-NIH-BEST (Biomarkers, Endpoints, and other Tools) Resource for a definition of *endpoint*, available at https://www.ncbi.nlm.nih.gov/books/NBK338448/.

[52] See the CDER Patient-Focused Drug Development web page, available at https://www.fda.gov/drugs/development-approval-process-drugs/cder-patient-focused-drug-development.

[53] For further discussion, see the draft guidance for industry *Rare Diseases: Natural History Studies for Drug Development*.

[54] See the guidance for industry, Food and Drug Administration staff, and other stakeholders *Patient-Focused Drug Development: Methods to Identify What Is Important to Patients* (February 2022).

- In small sample sizes, it is important to distinguish outcomes from different participants as much as possible. Dichotomous endpoints (e.g., dichotomizing a continuous measurement) can result in loss of information and should be avoided whenever possible.

Sponsors should select endpoints considering the objectives of each clinical investigation in the context of the overall clinical development program. Endpoint selection, especially considerations related to novel endpoints (that could be clinical outcomes or biomarkers as surrogate endpoints), is an important aspect of rare disease drug development. Sponsors are encouraged to engage early with the Agency to discuss endpoint development. Clinical investigations within a drug development program generally build upon the knowledge gained in early studies to guide the design and endpoint selection for later stages of development. Exploratory evidence from earlier phase clinical investigations may help inform the choice of dose and timing of endpoints.

Different endpoints are often appropriate for the evolving objectives of successive clinical investigations. Although the earliest clinical investigations will usually focus on safety assessments, they also can be useful in evaluating a drug's pharmacokinetics and assessing pharmacodynamic effects. Ideally, sponsors should conduct early- and mid-phase investigations (e.g., phase 2 clinical investigations, dedicated pharmacokinetic/pharmacodynamic studies) to guide selection of dose and frequency and can rely on pharmacodynamic or intermediate clinical effects, which may be assessed earlier than more definitive endpoints.[55] Additionally data from initial rare disease drug development in animal models may help to identify biomarkers to be used as candidate surrogate endpoints. Leveraging data from natural history or registry-based studies of rare diseases may also help to identify clinically relevant endpoints as well as to examine the relationship between disease severity/progression and the biomarker changes (e.g., to provide initial support for a surrogate endpoint). In general, late-phase clinical investigations are designed to provide clear determinations of efficacy and further evaluation of safety. FDA acknowledges that in rare disease drug development, the size of the population may prevent traditional early-, mid-, and late-phase clinical investigations. Other types of studies conducted early in drug development, including natural history or registry-based studies and use of animal models, can provide important information for later stages. FDA encourages sponsors to engage early with the Agency to discuss their drug development program to ensure learnings from earlier phases can be carried forward and adapted throughout a drug development program.

Sponsors should also consider the characteristics of an endpoint for the full range of participants, including all ages, affected races, ethnicities, and sexes to be enrolled into a clinical investigation. For rare diseases, practical considerations may warrant inclusion of a broad range of disease stages (e.g., severity of manifestations, development of manifestations secondary to long-standing primary disease manifestations) or phenotypes. The validity, sensitivity, reliability, or interpretability of an endpoint may be different for patients with mild, early-stage, or slowly progressive forms of a disease compared to patients with severe, late-stage, or rapidly

[55] See the guidance for industry *Population Pharmacokinetics* (February 2022).

progressive forms of the same disease.[56] These differences in characteristics of rare disease conditions can have effects on aspects of clinical investigation design (e.g., power) and endpoint interpretation. For considerations related to the patient population and enrollment criteria for a particular study endpoint in a rare disease drug development program, sponsors should communicate with the relevant review division.

Sponsors should consider approaches to clinical investigation design and assessment procedures that may improve the evidence supporting the rationale that an assessment is fit for purpose and the standardization/interpretability of assessment tools.[57] For example, qualitative interviews with clinicians can improve the quality of clinician-reported outcome measures, and detailed descriptions of procedures and training for performing assessments may improve accuracy and intra-reader and inter-reader reliability. It is possible for sponsors to assess the adequacy or success of blinding at the end of a clinical investigation.[58] Effective blinding of treatments can reduce concern about bias in the subjective aspects of an assessment (e.g., participant motivation), as can conduct of endpoint evaluation by raters not involved in other aspects of the clinical investigation (e.g., radiologists, exercise testers). Another consideration is that rare disease clinical development programs are often multinational, and sponsors should consider the effects of language, culture, and customs on the interpretability and relevance of outcome assessments.

Sponsors considering the development of novel clinical outcome assessments should identify and characterize these assessments early in their drug development programs. FDA advises sponsors to consider using or modifying existing measures for the disease under study because evaluating novel measures is time consuming, with potential unexpected outcomes, and evaluations initiated late in the process could delay drug development. FDA acknowledges that sometimes use of an existing endpoint measure is not feasible. Therefore, creation of a novel clinical outcome assessment may be necessary. At meetings with FDA, sponsors should discuss the availability and modification of existing clinical outcome assessments; such discussions should take place as early as possible in the drug development program. Furthermore, it is important to consider that the appropriateness of a clinical endpoint or clinical outcome assessment is context dependent, and endpoints that might be appropriate for some patients with a rare disease may not be appropriate for all patients with that rare disease, for patients with other rare diseases, or for patients with common diseases.

The following should also be considered for endpoint selection in rare disease clinical investigations:

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[56] See the draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products*.

[57] See the draft 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* (June 2022). When final, this guidance will represent the FDA's current thinking on this topic.

[58] See the guidance for industry *Placebos and Blinding in Randomized Controlled Cancer Clinical Trials for Drug and Biological Products* (August 2019).

- Selecting the appropriate endpoint (and timing of endpoint assessment) in a specific drug development program, such as a clinical endpoint that directly measures patient benefit or a surrogate endpoint that is not a direct measure of clinical benefit. In cases where using clinical endpoints is not feasible because changes in symptoms and disease status occur too slowly to be measured in a clinical investigation of reasonable duration, surrogate endpoints may be considered.[59]

- Estimating the magnitude of effect that may provide clinically meaningful benefit.

Additionally, FDA recognizes that for diseases that are very rare or have very slow and variable progression over years, the use of clinical endpoints may be challenging. In these situations, several strategies may be considered, such as using data from natural history or registry-based studies, to identify clinically relevant changes that are most prominent and most rapidly progressive that could serve as the basis for a clinical endpoint. Another strategy is to consider early development work on biomarkers as surrogate endpoints that may support approval (either for traditional or accelerated approval). Initial evaluation of the literature to identify such biomarkers, early work on translational animal models, and leveraging data from natural history cohorts before initiation of clinical development is essential. An early focus on developing a broad package of information, including genetic, in vitro, animal model, clinical data in patients with the disease, and eventually clinical pharmacodynamic (PD) data from early clinical investigations with the drug, can contribute to substantiate the use of the proposed biomarker as a surrogate. Sponsors are encouraged to request initial discussions with FDA (e.g., pre-IND) when they have a well-developed strategy and initial information on a proposed surrogate endpoint in drug development programs.[60]

D. Safety Evaluation

Evaluating whether a drug is safe involves weighing whether the benefits of the drug outweigh its risks under the conditions of use defined in labeling. Ultimately, what is a feasible and sufficient safety assessment is a matter of scientific and regulatory judgment based on the particular challenges posed by each drug and disease, including patients' tolerance and acceptance of risk in the setting of unmet medical need and the benefit offered by the drug.[61] A higher degree of uncertainty is common in drug development programs for rare diseases, where the prevalence of disease, and consequent limitations of study size, can limit the precision of safety and efficacy characterizations.[62] FDA recognizes that when a drug is developed to treat

[59] See the draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products*.

[60] See *SOPP 8101.1: Regulatory Meetings with Sponsors and Applicants for Drugs and Biological Products* (March 2023) for information on types of FDA meetings.

[61] See the guidance for industry *Determining the Extent of Safety Data Collection Needed in Late-Stage Premarket and Postapproval Clinical Investigations* (February 2016).

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

serious diseases for which there are few or no approved therapies, greater uncertainty or greater risks may be acceptable provided that the substantial evidence standard has been met.

Regulations do not specify the needed evidence of safety, except that the evidence must include adequate tests by all methods reasonably applicable.[63] 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) (ICH E1A) describes expected exposure for chronically used drugs for non-life-threatening conditions, but these expectations do not apply to the many rare diseases that are life threatening. Although ICH E1A does not mention rare diseases, the guidance states that a smaller number of patients may be acceptable when the intended treatment population is small.

E. Additional Considerations Related to Clinical Development for Rare Disease Drugs

Evidence-based decisions about what is feasible in terms of rare disease drug clinical investigation enrollment depend on accurately estimated disease prevalence.[64] Many rare diseases are genetic in origin and characterized by more than one phenotypic subtype (e.g., infantile, juvenile, adult). Prevalence estimates should include all phenotypic subtypes of a disease anticipated to respond to the investigational drug. Sponsors should determine prevalence estimates for countries in which clinical investigation sites are being considered. If prevalence estimates are anticipated to vary across countries, sponsors should evaluate the potential differences in prevalence estimates. Sponsors should provide the individual sources of current published prevalence estimates, rather than calculated averages, because published prevalence estimates can vary widely depending on clinical investigation details (e.g., case definition), country or region, and advances in diagnostics and treatment over time. To facilitate discussion with the review division about a feasible clinical investigation population enrollment goal, submissions should include complete citations and, if possible, a copy of each reference pertaining to the prevalence estimate.

FDA encourages sponsors to discuss their overall plans for maximizing the quantity and quality of safety and efficacy data in early drug development meetings with FDA. This may include approaches such as the following:

[63] See the guidance for industry *Premarketing Risk Assessment* (March 2005).

[64] The term *prevalence* is used here in the context of a database for clinical development program, not in the context of orphan-drug designation. Information about prevalence in orphan-drug designation can be found on the FDA's Designating an Orphan Product: Drugs and Biological Products web page, available at https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/default.htm.

- Decentralized clinical investigations: Decentralized clinical investigations may enhance convenience for clinical investigation participants by enabling remote participation. Decentralized clinical investigations reduce the burden on caregivers and facilitate research on rare diseases and diseases affecting populations with limited mobility or access to traditional clinical investigation sites. This may help improve clinical investigation participant engagement, recruitment, enrollment, and retention of a meaningfully diverse clinical population.[65]

- Natural history: Knowledge about a disease's natural history can inform many important aspects of clinical investigations, including planning for disease-specific challenges to patient accrual and retention to increase the size of the dataset. Robust natural history data can also help distinguish drug-related adverse events from underlying disease manifestations.[66]

- Clinical investigation eligibility: For rare diseases, it is especially important that inclusion and exclusion criteria do not unnecessarily constrain patient eligibility not only for patient accrual but also for an adequate representation of the safety in the intended treatment population. However, when appropriate, sponsors should consider enrichment strategies to decrease heterogeneity (nondrug-related variability) and to enhance the ability of the clinical investigation to identify safety risks of the drug and demonstrate a potential treatment effect.[67] Many rare diseases severely affect children, and for diseases that affect both children and adults, sponsors should explore early inclusion of pediatric participants in clinical studies and discuss their plans for pediatric enrollment with FDA during early stages of drug development, including pre-IND meetings.[68,69]

- Dose selection: Data-driven dose selection is important to avoid participant discontinuations because of unnecessary toxicity (dose too high) or lack of efficacy (dose too low), especially when only one registration clinical investigation is feasible. Consider using data from animal models of disease for different doses, a range of exposure response, intrapatient dose escalation studies, or quantitative modeling approaches (e.g., physiologically based pharmacokinetic or pharmacokinetic/pharmacodynamic modeling) to facilitate dose selection.

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[65] See the draft guidance for industry, investigators, and other stakeholders *Decentralized Clinical Trials for Drugs, Biological Products, and Devices* (May 2023). When final, this guidance will represent the FDA's current thinking on this topic.

[66] See the draft guidance for industry *Rare Diseases: Natural History Studies for Drug Development.*

[67] See the guidance for industry *Enrichment Strategies for Clinical Trials to Support Determination of Effectiveness of Human Drugs and Biological Products*.

[68] See 21 CFR part 50, subpart D, Additional Safeguards for Children in Clinical Investigations.

[69] See the draft guidance for industry *Rare Diseases: Early Drug Development and the Role of Pre-IND Meetings* (October 2018). When final, this guidance will represent the FDA's current thinking on this topic.

- Comparator arm: Sponsors should use a concurrent comparator arm design (e.g., placebo, no treatment, standard of care, active drug, multiple doses), employing randomization and blinding/masking whenever ethically and practicably feasible, to facilitate interpretation of results, including adverse event causality, especially with respect to the incidence and severity of adverse events that could be a manifestation of the disease under study.

- Clinical investigation conduct and data quality: Sponsors should ensure appropriate clinical investigation conduct and high data quality. This should include steps to prevent missing data, as even a small amount of missing data can impact the reliability of results. Sponsors should also maintain confidentiality of interim results while the clinical investigation is ongoing.

- Auxiliary cohorts: Depending on details of the clinical development program, the following approaches may augment the safety and efficacy database if the sponsor rigorously collects and analyzes the data:

  - A clinical investigation protocol with a safety cohort running parallel to the efficacy clinical investigation: This cohort would include patients with the disease who investigators think might benefit from the investigational drug but who do not meet all the registration clinical investigation eligibility criteria. Such patients can be enrolled in the clinical investigation, avoiding the need for a separate clinical investigation and protocol. However, these patients are not randomized and are excluded from the efficacy analysis. The ability to reliably evaluate outcomes from nonrandomized data sources can be limited.

  - Patients receiving drugs under expanded access:[70] Systematic collection of expanded access safety data might identify important premarketing signals that might otherwise not be observed until the drug is used in the more diverse practice setting. Plans for the use of these cohorts in a drug development program should be discussed early in the development process with the review division.

  - Relevant data from other sources, such as clinical investigations using the drug for other indications or studies of similar drugs.[71]

[70] See the draft guidance for industry *Expanded Access to Investigational Drugs for Treatment Use — Questions and Answers* (November 2022). When final, this guidance will represent the FDA's current thinking on this topic.

[71] New drug applications must include a "description and analysis of any other data or information relevant to an evaluation of the safety and effectiveness of the drug product obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from clinical investigations, including controlled and uncontrolled studies of uses of the drug other than those proposed in the NDA, commercial marketing experience, reports in the scientific literature, and unpublished scientific papers" (21 CFR 314.50(d)(5)(iv)). If an applicant relies on FDA's finding of safety or effectiveness for another drug or uses information to which it does not have a right of reference to fulfill a requirement for approval or licensure, FDA will not be able to consider the marketing application as a *stand-alone* application.

Sponsors should maintain communication with FDA throughout the development program to discuss potential required studies to collect additional efficacy data, such as postmarketing studies, and risk mitigation strategies. This can help avoid preventable delays in approving a safe and effective drug for patients with unmet medical need.[72] For additional information, refer to section VIII., Interactions With FDA.

VI. PHARMACEUTICAL QUALITY CONSIDERATIONS

Drug manufacturing should undergo development concurrently with clinical development. Review divisions encourage sponsors to discuss pharmaceutical quality development plans in early-phase meetings (such as at pre-IND meetings[73]) and throughout drug development to decrease the potential for developmental or approval delays related to drug manufacturing.

FDA recommends that the sponsor carefully assess any planned changes to the drug substance or drug product manufacturing process, analytical methods, or drug product formulation at any phase of development to determine if the changes could affect the safety or efficacy of the drug. These assessments may include analytical studies, nonclinical studies, and clinical investigations. These assessments should be conducted with each change and could inform whether bridging studies will be needed. Sponsors should design adequate testing procedures early and implement them in a timely manner to mitigate delays. To allow time to evaluate the potential effect of manufacturing changes on drug safety and effectiveness and to minimize possible delays in development, manufacturing changes should be made as early as feasible, and sponsors should use quality risk management.[74,75]

FDA may exercise some flexibility on the type and extent of manufacturing information that is expected at the time of submission and approval for certain components (e.g., stability data updates, process validation strategies, inspection planning, manufacturing scale-up). FDA can explore the level of flexibility on a case-by-case basis after considering factors such as (1) product characteristics, (2) seriousness of the condition and medical need, (3) manufacturing processes, (4) the robustness of the pharmaceutical quality system, and (5) the strength of the sponsor's risk-based quality assessment.

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[72] See the guidances for industry *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment* (March 2005) and *REMS: FDA's Application of Statutory Factors in Determining When a REMS Is Necessary* (April 2019).

[73] See the draft guidance for industry *Rare Diseases: Early Drug Development and the Role of Pre-IND Meetings.*

[74] See FDA's Emerging Technology Program web page, available at https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/emerging-technology-program, and the CBER Advanced Technologies Team (CATT) web page, available at https://www.fda.gov/vaccines-blood-biologics/industry-biologics/cber-advanced-technologies-team-catt.

[75] See the draft guidance for industry *Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products* (July 2023). When final, this guidance will represent the FDA's current thinking on this topic.

The need for larger amounts of the drug during the product development process may lead to the need to modify manufacturing procedures and purification methods. FDA also recognizes that transfer of manufacturing responsibilities may occur after initial nonclinical studies and/or clinical investigations (e.g., from a single investigator to a company, from a small company to a large company), which may be a more common scenario for drugs for rare diseases. Any of these changes (even changes expected to be minor) might result in unanticipated changes to drug characteristics (e.g., drug impurities, physical-chemical characteristics of proteins, cell phenotype of cellular products). If significant differences are identified in drug characteristics after a manufacturing change compared with drug batches (or biological product lots) used in earlier nonclinical studies or clinical investigations, then additional nonclinical studies and clinical investigations may be needed because these differences can raise concerns that the knowledge gained from the earlier studies will not apply to further use of the drug. Some examples of the many ways a change in drug characteristics may affect drug development include the following:

- The type, number, and level of impurities in a drug used in clinical investigations and for commercial distribution should be comparable to the drug batches used in toxicology studies. Changes might raise concerns that the drug used in later clinical investigations has unknown toxicological characteristics. Additional toxicology studies may be needed to evaluate the newly produced drug, delaying the clinical development program.

- Changes in critical quality attributes of the planned commercial drug after the clinical investigations might raise concerns that the safety and effectiveness findings of the clinical investigations do not apply to the newly manufactured drug. These concerns could warrant additional studies (nonclinical, clinical, or both) to address the concern before marketing approval.

Given the wide variety of drugs, some of which are complex, FDA advises sponsors to consult relevant guidances for industry (see sections III through V for a list of selected guidances).

VII. ADDITIONAL CONSIDERATIONS

A Participation of Patients, Caregivers, and Advocates

FDA encourages involvement of patients, their caregivers, and advocates in rare disease drug development.[76] Patient input can provide important information about patients' experiences, perspectives, needs, and priorities that can be incorporated throughout the drug development process. This engagement can take many forms, such as providing solicited consultation on scientific issues (e.g., clinically meaningful treatment effects), working with industry sponsors as they design and conduct clinical investigations, and contributing to patient-focused drug

[76] FDA can provide support for patients, caregivers, and advocates through interactions with FDA staff and offices (e.g., CDER's Professional Affairs and Stakeholder Engagement team, CDER's Patient Focused Drug Development, the Center for Biologics Evaluation and Research (CBER) Patient Engagement Program, and the Office of Commissioner's Patient Affairs Staff).

development initiatives.[77] For drugs in development, FDA is subject to strict confidentiality requirements and may not be able to discuss with the public specific information about a drug development program.[78] In these situations, FDA encourages direct sponsor-patient communication, when feasible, to facilitate the incorporation of patient perspectives and experiences into the drug development process.

B. Expedited Programs

Many rare diseases are serious or life-threatening disorders with unmet medical needs. Therefore, drugs treating these diseases may qualify for one or more expedited programs. FDA encourages sponsors to consider these programs, which include fast-track designation, breakthrough therapy designation, and accelerated approval. For details on eligibility and applications for expedited program designation, sponsors should consult the guidances for industry *Expedited Programs for Serious Conditions — Drugs and Biologics* (May 2014) and *Expedited Programs for Regenerative Medicine Therapies for Serious Conditions* (February 2019).

C. Pediatric Considerations

According to estimates, about half of the people affected by rare diseases are children. Therefore, conducting studies to evaluate drugs in pediatric patients is critical for determining the safety and efficacy of medications for many rare diseases.[79,80] When preparing development plans, the sponsor should consider whether the rare disease affects children and adults or only children. The degree of overlap between pathophysiology and similarity of clinical outcomes is an important consideration in pediatric development when a disease is seen across the life span. In general, sponsors should include pediatric patients with rare diseases in premarketing clinical studies to develop data on the full range of people with the disease.

FDA strongly encourages sponsors to study the drug in all relevant pediatric populations, birth to younger than 17 years of age, so that the drug can be properly and completely labeled for pediatric use. As part of these pediatric studies, FDA encourages sponsors to develop pediatric

[77] See the draft guidance for industry and other stakeholders *Developing and Submitting Proposed Draft Guidance Relating to Patient Experience Data* (December 2018). When final, this guidance will represent the FDA's current thinking on this topic. For more information, see the web page Learn About FDA Patient Engagement, available at https://www.fda.gov/ForPatients/PatientEngagement/default.htm#PFDD_2.

[78] For example, see 21 CFR 314.430.

[79] 21 CFR 201.57(c)(9)(iv)(A) defines "pediatric population(s)" and "pediatric patient(s)" as "the pediatric age group, from birth to 16 years, including age groups often called neonates, infants, children, and adolescents."

[80] For the purposes of pediatric drug development, FDA interprets "birth to 16 years" in 21 CFR 201.57(c)(9)(iv)(A) to mean from birth to before the 17th birthday (i.e., birth through 16 years of age).

formulations of the drug to enable accurate dosing, down to the youngest children affected by the rare disease.[81]

For studies in which both pediatric and adult participants are included, the sponsor should consider the relevance and comparability of endpoints to both groups, including whether results from both groups can be combined in a single statistical analysis. Importantly, there are additional safeguards for pediatric participants enrolled in clinical studies beyond those provided for adult participants.[82] These additional safeguards could limit the use of some procedures in children that would be acceptable for adults. Careful planning for a drug being developed to treat a rare disease in children is important to maximize the efficiency and increase the likelihood of success of the drug's clinical development program. Such planning should include discussions with FDA early in drug development about the epidemiology of the rare disease and plans for inclusion of pediatric participants in clinical studies.[83,]

VIII. INTERACTIONS WITH FDA

FDA offers sponsors numerous opportunities for interaction. When developing an investigational drug for a rare disease, FDA encourages sponsors to meet with the relevant drug review division supporting development of that particular drug early in the development program.[84] FDA's early feedback to sponsors may result in more efficient drug development. At the sponsor's request, FDA will, if possible, provide advice on specific matters relating to an IND, including advice on the adequacy of data to support an investigational plan, the design of a clinical investigation, and whether proposed investigations are likely to produce the data and information needed to meet requirements for a marketing application.[85] FDA provides formal advice through milestone meetings (e.g., pre-IND meeting, end of phase 2 meeting).

In addition, CDER's Critical Path Innovation Meetings (CPIM) program provides a nonbinding and informal forum for investigators from industry, academia, patient advocacy groups, and government to obtain general advice on methodologies or technologies and to discuss topics of

[81] See the draft guidance for industry *General Clinical Pharmacology Considerations for Pediatric Studies of Drugs, Including Biological Products* (September 2022). When final, this guidance will represent the FDA's current thinking on this topic.

[82] See 21 CFR part 50, subpart D.

[83] See the draft guidance for industry *Pediatric Drug Development: Regulatory Consideration—Complying With the Pediatric Research Equity Act and Qualifying for Pediatric Exclusivity Under the Best Pharmaceuticals for Children Act* (May 2023) and the draft guidance for industry, sponsors, and IRB's *Ethical Considerations for Clinical Investigations of Medical Products Involving Children* (September 2022). When final, these guidances will represent the FDA's current thinking on this topic.

[84] See the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

[85] See the guidance for industry and review staff *Best Practices for Communication Between IND Sponsors and FDA During Drug Development* (December 2017).

interest independent of a specific drug development program.[86] In CPIMs, FDA staff members may provide general advice on how a technology or methodology might be used to enhance drug development. CBER participates in CPIM meetings when crosscutting issues arise that involve both centers. CPIM discussions are nonregulatory and nonbinding on both FDA and CPIM requesters.

In addition, the INitial Targeted Engagement for Regulatory Advice on CBER/CDER ProducTs (INTERACT) meetings are intended for novel questions and unique challenges in early development (i.e., prior to filing of an IND). The advice provided by the FDA staff to a potential sponsor during an INTERACT meeting may help streamline development by, for example, helping sponsors avoid unnecessary preclinical studies.[87]

Additional information about rare disease drug development programs can also be found at CDER's Accelerating Rare disease Cures (ARC) Program website,[88] CDER's Rare Diseases Team website,[89] and CBER's Rare Disease Program website.[90] The Office of Orphan Products Development can be contacted for matters related to orphan product designation.

[86] See the guidance for industry *Critical Path Innovation Meetings* (April 2015).

[87] See *SOPP 8101.1: Regulatory Meetings with Sponsor and Applicants for Drugs and Biological Products*.

[88] Available at https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/accelerating-rare-disease-cures-arc-program.

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