Rare Diseases: Common Issues in Drug Development

Guidance for Industry

DRAFT GUIDANCE

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

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Rare Diseases
Revision 1

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Rare Diseases: Common Issues in Drug Development Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

I. INTRODUCTION

The purpose of this guidance is to assist sponsors of drug and biological products for the treatment or prevention of rare diseases in conducting more efficient and successful drug development programs.[2] Although 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, natural history data, and drug development experience.

This guidance revises and replaces the draft guidance for industry *Rare Diseases: Common Issues in Drug Development* issued in August 2015. This revision includes the following:

- Updates to the Natural History Studies section
- Inclusion of issues for evaluation and validation of surrogate biomarkers
- Description of nonclinical flexibility
- Additional information on external controls and early randomization
- Addition of a safety section

[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.

- Retitled Chemistry, Manufacturing, and Controls section to Pharmaceutical Quality Considerations

- Additional information on changes to drug substance or manufacturing process with clarification on areas of flexibility

- Inclusion of an Additional Considerations section addressing several topics: participation of patients, caretakers, and advocates; consideration of pediatric issues; and interactions with FDA

This guidance addresses the importance of the following elements in development programs for rare diseases:[3]

- Adequate description and understanding of the disease's natural history

- Adequate understanding of the pathophysiology of the disease and the drug's mechanism of action

- Nonclinical-pharmacotoxicology and human toxicology considerations to support the proposed clinical investigation or investigations

- Selection or development of outcome assessments and endpoints

- Evidence to establish safety and effectiveness

- Drug manufacturing considerations during drug development (e.g., pharmaceutical quality system considerations)[4]

- Participation of patients, caretakers, and advocates in development programs

- Interactions with the Agency

Early consideration of these issues gives sponsors the opportunity to efficiently and effectively address the issues and to have productive meetings with FDA. These and other issues, as they apply to all drug development programs, are also considered in FDA and International Council for Harmonisation (ICH) guidances for industry (see References for selected guidances).

[3] For recommendations on human gene therapy for rare diseases, see the draft guidance for industry *Human Gene Therapy for Rare Diseases* (July 2018). 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/RegulatoryInformation/Guidances/default.htm.

[4] See the ICH guidance for industry *Q10 Pharmaceutical Quality System* (April 2009) and the guidance for industry *Process Validation: General Principles and Practices* (January 2011). We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

This guidance does not contain discussion of the general issues of statistical analysis or clinical trial design. Those topics are addressed in the ICH guidances for industry *E9 Statistical Principles for Clinical Trials* (September 1998) and *E10 Choice of Control Group and Related Issues in Clinical Trials* (May 2001), respectively.

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

The Orphan Drug Act (the ODA) generally defines a rare disease or condition as one affecting fewer than 200,000 people in the United States.[5] Most rare diseases, however, affect far fewer people. The ODA created a process for the Agency to designate a drug as a drug for a rare disease or condition. The sponsor of a drug holding orphan drug designation may be eligible for certain financial incentives intended to help make developing drugs for small numbers of patients financially viable;[6] however, the ODA does not create a statutory standard for the approval of orphan drugs that is different from the standard for approval of drugs for common conditions. Approval of any drug — for either a rare 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. Sponsors should obtain evidence of effectiveness in an identified population from adequate and well-controlled studies (see section VII., Evidence of Safety and Effectiveness).[7] FDA regulations provide flexibility in applying regulatory standards because of the many types and intended uses of drugs. 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.[8] This flexibility extends from the early stages of development to the design of adequate and well-controlled studies required to demonstrate effectiveness to support marketing approval and to establish safety data needed for the intended use.

[5] See Public Law 97-414, 96 Stat. 2049 et seq. (1983) as amended by Public Law 98-551, 98 Stat. 2815, 2817 (1984), which added a numeric prevalence threshold to the definition of rare diseases. The ODA also defines a rare disease 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." Section 526(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bb(a)(2)(B)).

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

[7] See 21 CFR 314.126.

[8] 21 CFR 314.105(c).

III. NATURAL HISTORY STUDIES

A. 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 if it is sufficient to inform their drug development programs. A natural history study initiated early may run in parallel with early stages of drug development — including preclinical drug development — and may allow updating of drug development strategies as new learning emerges.

An in-depth understanding of the disease can help sponsors with the following:

- Define the disease population, including a description of the full range of disease manifestations and identification of important disease subtypes. This may allow selection of patients more likely to progress and develop the endpoints assessed in the context of a clinical trial (prognostic enrichment).

- Understand and implement critical elements in clinical trial design, such as trial duration and entry criteria.

- Select clinical endpoints and develop sensitive and specific outcome measures.

- Identify new or validate existing biomarkers that may provide proof-of-concept (POC) information, guide dose selection, allow screening for possible responders (predictive enrichment), allow early recognition of safety concerns, or provide supportive evidence of efficacy. In some cases, sponsors can use biomarkers as surrogate endpoints.[9]

In special circumstances, such as when it may be impractical or unethical, a well-designed and conducted natural history study can provide an external control group for interventional trials.[10]

No single set of natural history study data elements adequately describes all rare diseases. Rare diseases are highly diverse, may affect many organ systems and have wide variations in the rates and patterns of manifestations and progression. General principles that enhance the usefulness of natural history studies in rare disease drug development include the following:

[9] See the guidance for industry *Expedited Programs for Serious Conditions — Drugs and Biologics* (May 2014).

[10] See the ICH guidance for industry *E10 Choice of Control Group and Related Issues in Clinical Trials*.

- Conduct a study of sufficient duration to capture clinically meaningful outcomes and variability in the course of the disease.

- Select data elements based on features of the disease, including signs and symptoms that are most important to patients (i.e., disease aspects most likely to be life limiting or life altering), potential prognostic characteristics, and disease features that may help formulate a sensitive clinical endpoint.[11] A sponsor should determine when specific disease manifestations are likely to develop and are likely to persist.

- Collect data from clinical examination findings, laboratory measurements, imaging, reports of patient functioning and feeling,[12] and other relevant sources. The frequency of data collection is informed in part by knowledge of disease characteristics, such as the rate of deterioration of a patient condition and the presence or absence of exacerbations of a disease. Data should include the standards of care and concomitant therapies. A sponsor can modify the type and extent of data collection in a natural history study based on accumulated knowledge as the study proceeds.

- Include patients across a wide spectrum of disease severity and phenotypes, rather than focus on a particular subtype. Broad inclusion criteria can allow identification and better characterization of disease phenotypes for which therapy development may be more feasible or needed.

- Use standardized collection methods and medical terminology to enhance the value and usefulness of natural history study data.

We encourage making data from natural history studies publicly available to support and promote rare disease drug development.

See section VII., Evidence of Safety and Effectiveness, for discussion of natural history studies as a source of data for historically controlled clinical trials.

B. Types of Natural History Studies

Natural history study designs can be characterized as (1) retrospective or prospective and (2) cross-sectional or longitudinal.

1. Retrospective and prospective studies differ with respect to when patient data are collected. The information to be collected in the study is typically set forth in a protocol or procedure manual.

[11] See the draft guidance for industry, FDA staff, and other stakeholders *Patient-Focused Drug Development: Collecting Comprehensive and Representative Input* (June 2018). When final, this guidance will represent the FDA's current thinking on this topic.

[12] See the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (December 2009).

- Retrospective natural history studies most commonly use information in existing medical records (e.g., patient charts). The included patients have defined characteristics such as diagnoses and outcomes.

- Prospective natural history studies collect and analyze new data generated from identified patients at specified time points after the natural history study has been initiated.

2. Cross-sectional and longitudinal natural history studies collect data from cohorts of patients. Cross-sectional and longitudinal studies may be retrospective or prospective.

   - Cross-sectional natural history studies collect data from individual patients at a single point in time. The point in time may be a specific date or set by stage of illness, date of diagnosis, onset of certain sign and symptoms, or other criteria.

   - Longitudinal natural history studies collect data from patients with the identified condition over time. The length of time and frequency of data collections can vary considerably and should be tailored to the characteristics of the disease.

Each type of natural history study has advantages and disadvantages. In general, retrospective studies may be conducted more quickly than prospective studies. However, retrospective studies are limited in that they can only obtain data elements available in existing records. Retrospective studies are also limited by many factors including but not limited to inconsistent measurement procedures, irregular time intervals, and unclear use of terms that may limit the completeness and generalizability of the information. These limitations often preclude the use of such studies as an external control group for drug trials if it is not possible to match characteristics of patients in the drug trial with the historical controls. Prospective studies provide systematically and comprehensively captured data using consistent medical terms and methodologies relevant to future clinical trials.

For a prospective design, a cross-sectional study may be conducted more quickly than a longitudinal study. However, cross-sectional studies are unable to provide a comprehensive description of the course of progressive or recurrent disease. Cross-sectional studies may be helpful to inform the design of a longitudinal natural history study. Longitudinal studies typically yield the most comprehensive information about a disease, can characterize the course of disease within patients, and can help distinguish different phenotypes.

IV. DISEASE PATHOPHYSIOLOGY, CLINICAL MANIFESTATIONS, AND IDENTIFICATION AND USE OF BIOMARKERS

Knowledge about a disease's pathophysiology and clinical manifestations over time, which is frequently incomplete for rare diseases, can be invaluable to the successful development of a treatment, for example, by:

- Identifying clinical manifestations of the disease that may have greater or earlier responsiveness to treatment

  - Manifestations that are more closely linked to the disease pathophysiology and that are targeted by the drug's mechanism of action may be more likely to lead to clinical benefits, especially if those manifestations are earlier in the disease course, when intervention may be more beneficial.

- Estimating the amount of effect that may provide clinically meaningful benefit

- 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 trials 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 treatment in 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.[13]

  - For example, response of a laboratory measurement sensitive to drug effect could be used to screen potential responders for inclusion in efficacy trials. Sponsors may also be able to identify clinical or genomic characteristics that predict response using these biomarkers.

For special considerations related to use of biomarkers as surrogate endpoints, see section VI., Efficacy Endpoints.

A surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign, or other measure, that is thought to be able to predict clinical benefit but is not itself a measure of clinical benefit.[14] Effects on some surrogate endpoints (e.g., blood pressure, low-density lipoprotein cholesterol) are well established predictors of clinical benefit for certain indications and are regularly used as the basis for traditional approval of drugs. Less well established surrogate endpoints, but which are considered reasonably likely to predict clinical

[13] See the draft guidances for industry *Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products* and *Adaptive Design Clinical Trials for Drugs and Biologics* (December 2012). When final, these guidances will represent the FDA's current thinking on these topics.

[14] See the guidance for industry *Expedited Programs for Serious Conditions—Drugs and Biologics*. See also the definition of *surrogate endpoint* in section 507(e)(9) of the Federal Food, Drug, and Cosmetic Act and the definition developed by the BEST (Biomarkers, EndpointS, and other Tools) Resource, which states that a *surrogate endpoint* is an "endpoint that is used in clinical trials as a substitute for a direct measure of how a patient feels, functions, or survives. A surrogate endpoint does not measure the clinical benefit of primary interest in and of itself, but rather is expected to predict that clinical benefit or harm based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence." See the BEST Resource at https://www.ncbi.nlm.nih.gov/books/NBK326791/.

benefit, may be used as a basis for accelerated approval for treatment of serious or life-threatening diseases.

Most rare diseases are serious or life threatening, and patients with rare diseases may have no available therapies for the disease. Section 506(c) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) provides that FDA may grant accelerated approval to:

> . . . a product for a serious or life-threatening disease or condition . . . upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments.[15]

The use of a surrogate endpoint requires demonstration of analytical and clinical validation of the biomarker test.

The analytic validity should be confirmed *before* starting the clinical trial. Analytical validation evaluates several factors including the following:

- Sensitivity of the assay
- Specificity of the assay to measure the biomarker
- Range of results that can be measured
- Standardized methods of sample collection, shipment, and preparation
- Reproducibility of the results

The guidance for industry and FDA staff *Qualification Process for Drug Development Tools* (January 2014) includes important information about the features of biomarkers used as endpoints.[16] For advice about biomarker development within a specific drug development program, the sponsor should request advice from the appropriate review division.[17] In addition, the Center for Drug Evaluation and Research's (CDER's) Critical Path Innovation Meetings program provides a forum to obtain general advice on methodologies or technologies such as biomarkers to enhance drug development.[18]

[15] Section 506(c)(1)(A) of the FD&C Act (21 U.S.C. 356(c)(1)(A)).

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

[17] 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.

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

V. NONCLINICAL STUDIES

Nonclinical studies are a mandated part of drug development.[19] 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."[20] Nonclinical studies can also contribute to a better understanding of the drug's possible efficacy, mechanism of action, pharmacokinetics, and metabolism. The data generated from nonclinical studies are important to the design of early phase clinical trials, 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 toxicologic profile.

Internationally accepted guidances discuss the general design of nonclinical safety studies and the timing of such studies relative to the conduct of a clinical development program.[21] Regulations state that it is appropriate for FDA to exercise the broadest flexibility in applying the statutory standards, while preserving appropriate guarantees for safety and effectiveness, for drugs to treat serious and life-threatening diseases.[22] This flexibility includes determining the nonclinical data necessary to support clinical development programs. 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 anticipated risks to humans, and the existing accumulated nonclinical toxicology and human data. When determining the relevance of existing data, a sponsor may consider factors such as drug product constituents, dosage form, route of administration, dose levels, and dosing regimen plan.

For serious or life-threatening diseases where current treatments, if any, are inadequate, clinical trials can often proceed with a modified nonclinical development program described in guidances on nonclinical studies.[23] However, these trials may proceed only under limited circumstances, with sufficient justification, and when no specific safety concern is present. For example, FDA could consider toxicology studies in a single species or toxicology studies of less than chronic duration to be sufficient to support clinical development. The ICH guidances for

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

[20] Ibid.

[21] 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); *S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* (July 1997); and *S9 Nonclinical Evaluation for Anticancer Pharmaceuticals* (March 2010). See also the draft guidance for industry *Investigational Enzyme Replacement Therapy Products: Nonclinical Assessment* (May 2015). When final, this guidance will represent the FDA's current thinking on this topic.

[22] See 21 CFR 312.80.

[23] See the guidances for industry ICH M3(R2), ICH S6(R1), and ICH S9.

industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* (January 2010) and *S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* (July 1997) outline chronic toxicology studies to support clinical indications of chronic, lifetime use. A chronic toxicity study calls for a 6-month duration of dosing in a rodent and a 9-month duration of dosing in a nonrodent species. If chronic toxicology studies are required, the sponsor may be able to conduct them concurrently with clinical trials or in a staggered fashion, such that the resulting data from these studies are submitted before dosing of any patient in an ongoing clinical trial that exceeds the duration of the available nonclinical data. Sponsors should justify the use of such an approach. In some cases, the sponsor may be able to delay submission of certain nonclinical studies to a marketing application (e.g., reproduction and developmental toxicology studies) or defer submission to the postmarketing period (e.g., carcinogenicity studies). FDA strongly encourages a sponsor to discuss the proposed approach with the review division to obtain concurrence on any abbreviated or deferred nonclinical program that could support the proposed clinical trials.[24]

The sponsor should base the design of the pivotal toxicology studies on the biology of the disease, expected pharmacology of the drug, existing POC data, proposed population to be studied (e.g., adult versus pediatric), and proposed clinical trial design(s) for the clinical indication being sought. Generally, healthy animals are the test system used in traditional toxicology testing and, in most circumstances, should be the test system used to support clinical trials. 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 disease have been utilized in limited situations such as enzyme replacement therapy. Toxicology testing in an animal model of disease may contribute to the nonclinical support for clinical trials but usually will not substitute for toxicology testing in healthy animals.[25] 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.

When clinical trials are to be conducted in pediatric patients, POC data is required to establish a prospect of direct benefit to the pediatric population.[26] Robust animal model results may support the possibility of clinical benefit and the potential for a favorable benefit-risk assessment. For many rare diseases, however, 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. Sponsors can submit data from relevant in vitro models as supportive information.

[24] 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).

[25] The FDA encourages sponsors to consult with review divisions when considering nonanimal testing methods believed to be suitable, adequate, validated, and feasible. The FDA will consider if the alternative method could be assessed for equivalency to an animal test method.

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

FDA encourages the sponsor to communicate early in the drug development process with the review division to discuss an appropriate nonclinical development program for the investigational drug.

VI. EFFICACY ENDPOINTS

The selection of appropriate endpoints is critical for a clinical trial. For many rare diseases, well-characterized efficacy endpoints appropriate for the disease are not available. To define a trial endpoint, a sponsor should select a patient assessment to be used as an outcome measure and define when in the trial the patient would be assessed.

Endpoint selection for a clinical trial 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 (see section III., Natural History Studies).

- 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 that could be assessed to evaluate the drug's effectiveness.

- The possibility of using the accelerated approval pathway.[27]

Despite continuing efforts to develop novel surrogate endpoints, currently, clinical outcomes as opposed to surrogate endpoints are the usual endpoints for the adequate and well-controlled trials (see section VII., Evidence of Safety and Effectiveness) that will provide the substantial evidence of effectiveness supporting marketing approval of the drug. Sponsors should select endpoints considering the objectives of each trial in the context of the overall clinical development program. Different endpoints are often appropriate for the evolving objectives of successive clinical trials. Although the earliest clinical investigations will usually focus on safety assessments, early investigations also can be useful in evaluating a drug's pharmacokinetics and assessing pharmacodynamic effects. Sponsors should conduct early- and mid-phase (e.g., phase 2) clinical investigations to guide selection of dose strength and frequency and can rely on pharmacodynamic or intermediate clinical effects, which may be seen earlier than more definitive endpoints. Late-phase clinical investigations are generally designed to provide clear determinations of efficacy and further evaluation of safety.

Clinical trials 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.

[27] For further discussion, see the guidance for industry *Expedited Programs for Serious Conditions — Drugs and Biologics*.

Exploratory evidence from earlier phase trials helps inform the choice of dose and timing of endpoints. However, adaptive seamless trial designs may allow early evidence to be used later in a study, especially helpful when there are limited numbers of patients to study.[28] If an adaptive design is under consideration, a thorough statistical analysis plan including the key features of the trial design and preplanned analyses should be discussed with the review division before trial initiation.

Treatment-assignment blinding is important to lessen the potential for bias in trial results, but ensuring perfect blinding is difficult for many treatments. An example of potential unblinding is when all patients receiving an experimental drug develop a certain side effect or requires a procedure/surgery, yet no patient in the placebo arm has the same side effect or procedure. When the primary endpoint is clinically meaningful but susceptible to individual interpretation, the trial may benefit from having additional supportive secondary endpoints (e.g., laboratory measurements). Additionally, use of performance outcome assessments (e.g., cognitive tests, ambulation tests), administered by trained health care professionals (blinded to treatment) and standardized across patients and sites, may complement reports from caregivers and patients regarding the relevant aspects of day-to-day functioning.

Sponsors should also consider the characteristics of an endpoint for the full range of patients, including pediatric patients, to be enrolled into a clinical trial. For rare diseases, practical considerations may warrant inclusion of a broader range of disease stages (e.g., severity of manifestations, development of manifestations secondary to long-standing primary disease manifestations) or phenotypes than might be used for trials in common diseases. 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 progressive forms of the same disease.

Sponsors should consider approaches to trial design and assessment procedures that may improve the utility of assessment tools. For example, a detailed description of procedures and training for performing the assessment may improve the reliability of the assessment. An assessment training program for investigators may improve both intra-rater and inter-rater consistency. It is possible for sponsors to assess the adequacy/success of blinding at the end of a trial. Effective blinding of treatments can reduce concern about bias in the subjective aspects of an assessment, as can conduct of endpoint evaluation by raters not involved in other aspects of the trial (e.g., radiologists, exercise testers). Another consideration is that rare disease clinical development programs are often multinational, and sponsors should consider the effect 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 assessment 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. At meetings with FDA,

[28] See the draft guidance for industry *Adaptive Design Clinical Trials for Drugs and Biologics* (September 2018).

sponsors should discuss the availability and modification of existing clinical outcome assessments.

VII. EVIDENCE OF EFFECTIVENESS AND SAFETY

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. In rare disease drug development, given the limited number of patients, it is crucial to standardize the collection and handling of data to ensure quality and interpretability. Increased measurement variability reduces power. Standardized operating procedures and quality assurance and quality control are essential. This is especially important when the trial is being conducted at multiple sites.

A. Effectiveness

One of the statutory requirements for drug marketing approval is "substantial evidence" that the drug will have its claimed effect.[29] This requirement is the same for all drugs regardless of whether they are for common or rare diseases. Substantial evidence is based on the results of adequate and well-controlled investigations.[30] 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 a disease, placebo effect, or biased observation."[31] Scientifically established essential elements that determine whether a trial is adequate and well-controlled are both required by regulation and generally recognized and accepted by the scientific community. Design features of an adequate and well-controlled trial protocol include the following:[32]

- A clear statement of the trial objectives, a statement and rationale regarding planned sample size, and a summary of the methods of analysis being used

- A design that permits a valid comparison with a control that may be concurrent (e.g., placebo, standard of care, active treatment, dose comparison) or, in limited and special circumstances, historical

[29] 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)).

[30] See 21 CFR 314.126(a). In some circumstances, data from one adequate and well-controlled clinical investigation and confirmatory evidence can be sufficient. See section 505(d) of the FD&C Act. See also the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998).

[31] 21 CFR 314.126(a).

[32] 21 CFR 314.126(b).

- Methods of patient selection that are well defined and result in the selection of an appropriate population for trial

- Methods that minimize bias in assigning patients to trial groups and ensure comparability between or among trial groups (e.g., randomization)

- Methods that minimize bias in trial conduct, outcome measures, and analysis (e.g., blinding techniques)

- Methods of assessment of patients' responses that are well defined and reliable (e.g., appropriate endpoints for the trial objectives).

- Methods of analysis adequate to assess effects of treatment (e.g., an appropriate statistical analysis plan).

B. Use of Historical Controls and Early Randomization

Ultimately, registration trials must be designed to demonstrate whether an observed beneficial effect is caused by the investigational intervention. Concurrent control designs and randomization minimize unknown variables that could affect the outcome independent of the intervention.

1. Historical (external) controls

For serious rare diseases with unmet medical need, interest is frequently expressed in using an external, *historical*, control in which all enrolled patients receive the investigational drug, and there is no randomization to a concurrent comparator group (e.g., placebo/standard of care). The inability to eliminate systematic differences between nonconcurrent treatment groups, however, is a major problem with that design. This situation generally restricts use of historical control designs to assessment of serious disease when (1) there is an unmet medical need;[33] (2) there is a well-documented, highly predictable disease course that can be objectively measured and verified, such as high and temporally predictable mortality; and (3) there is an expected drug effect that is large, self-evident, and temporally closely associated with the intervention. However, even diseases with a highly predictable clinical course and an objectively verifiable outcome measure may have important prognostic covariates that are either unknown or unrecorded in the historical data.

As discussed in section III., Natural History Studies, when concurrent controls are impractical or unethical, clinical trials can rely on a historical control. A natural history study providing systematically and comprehensively captured data using uniform medical language and methodologies relevant to the interventional clinical trials helps ensure that the historical control is comparable to the treatment group. Natural history studies should be part of earliest drug development. However, initiation of prospective natural history studies should not delay

[33] See the ICH guidance for industry *E10 Choice of Control Group and Related Issues in Clinical Trials*.

interventional testing otherwise ready to commence for a serious disease with unmet medical need.

2. Early randomization when feasible

In most cases, randomized controlled clinical trials are the most efficient and accurate way to determine whether a drug has a clinically meaningful effect on the disease being treated. Randomization of the first and all subsequently enrolled patients, including those in the earliest phases of clinical development, helps ensure that each patient's contribution is interpretable, avoiding potentially misleading findings from open-label, single-arm, externally controlled trials. Stratified randomization (e.g., by important prognostic factors such as age or disease severity) may be useful to improve comparability of trial groups.

Sponsors should explore and address concerns about control arms with patient and caregivers stakeholder groups and clinical investigators early in planning stages to avoid undermining trial recruitment and retention. Sponsors can sometimes address patient and family concerns by using modified trial designs, when appropriate, to demonstrate effectiveness and interpretation of safety signals. These designs retain the advantages of placebo-controlled trials 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).

In all cases, it is important for patient and family stakeholder group members to understand that because an investigational drug's effectiveness, like its safety, is unknown, the placebo or standard of care group may receive a net clinical benefit that is equal to or greater than that the group receiving the investigational drug.

C. Safety

The goal of safety evaluation during drug development is to characterize the drug's safety profile in a reasonable number of patients over a reasonable duration of time, consistent with the intended use of the drug. For the FDA, the term *reasonable* in the context of rare diseases means consideration of feasibility challenges posed by the limited number of patients with the disease.

FDA interprets reference in the FD&C Act to the *safety* of a drug for the uses recommended in labeling as meaning that the benefits of a drug outweigh its risks for those uses. 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 for risk in the setting of unmet medical need.[34]

[34] The term *sufficient* in this context refers to anticipated sufficiency in terms of trial enrollment. Whether a safety database is sufficient for FDA to conclude that the benefits of the drug exceed the risks is a marketing application review issue.

Regulations do not specify the needed evidence of safety, except that the evidence must include adequate tests by all methods reasonably applicable.[35] 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) 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.

Evidence-based decisions about what is feasible in terms of rare disease drug trial enrollment depend on accurately estimated disease prevalence.[36] 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 disorder anticipated to respond to the investigational drug. Sponsors also should determine prevalence estimates for all countries in which trial sites are being considered. Sponsors should provide the individual sources of current published prevalence estimates, rather than calculated averages, because published prevalence estimates can vary widely depending on study 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 trial safety 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 data in early drug development meetings with FDA. Several approaches for augmenting the safety assessment are discussed below. FDA encourages sponsors to propose additional strategies tailored to the specific challenges of their drug development programs.

- Natural history: As discussed in section III, Natural History Studies, knowledge about a disease's natural history can inform many important aspects of trials. From a safety perspective, this includes planning for disease-specific challenges to patient accrual and retention to maximize the size of the premarket safety dataset. Robust natural history data can also help distinguish drug-related adverse effects from underlying disease manifestations.

- Trial eligibility: For rare diseases, it is especially important that inclusion and exclusion criteria do not unnecessarily constrain patient eligibility for not only patient accrual but 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 trial

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

[36] The term *prevalence* is used here in the context of a safety database, 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.

to demonstrate a potential treatment effect.[37] Many rare diseases severely affect children, and for diseases that affect both children and adults, sponsors should explore early inclusion of pediatric patients in clinical studies.[38]

- Dose selection: Attention to dose selection is important to avoid patient discontinuations because of lack of efficacy (dose too low) or unnecessary toxicity (dose too high), especially when only one registration trial is feasible.

- Comparator arm: From a safety evaluation perspective, sponsors should use a concurrent comparator arm design (e.g., placebo, no treatment, standard of care, active drug, multiple doses), whenever ethically and practicably feasible, to facilitate interpretation of adverse event causality, especially with respect to the incidence and severity of adverse events that could be a manifestation of the disease under study.

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

  – A trial protocol with a safety cohort running parallel to the efficacy trial: 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 trial eligibility criteria. Such patients can be enrolled in the trial, avoiding the need for a separate trial and protocol. However, these patients are not randomized and are excluded from the efficacy analysis.

  – Patients receiving drugs under expanded access:[39] 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. Expanded access programs can also randomize participants to more than one dose or duration of therapy. Plans for these cohort should be discussed early in the development process with the review divisions.

  – Relevant data from other sources, such as trials using the drug for other indications or studies of similar drugs.[40]

[37] See the draft guidance for industry *Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products*. When final, this guidance will represent the FDA's current thinking on this topic.

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

[39] See the guidance for industry *Expanded Access to Investigational Drugs for Treatment Use — Questions and Answers* (October 2017).

[40] 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 new drug application, commercial marketing experience, reports in the scientific literature, and unpublished scientific papers." 21 CFR

Sponsors should maintain communication with FDA as safety data accrue because timely discussion of potentially needed postmarketing studies or risk mitigation measures beyond labeling and routine pharmacovigilance facilitates submission of a complete marketing application. This can help avoid preventable delays in access to an approved drug for patients with unmet medical need.[41] For additional information refer to section X., Interactions With FDA.

VIII. 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 (such as at pre-investigational new drug application (pre-IND) meetings) and throughout drug development to decrease the potential for developmental or approval delays related to drug manufacturing.[42]

FDA recommends that the sponsor carefully assess any planned changes to the drug substance or drug product manufacturing process or drug product formulation at any phase of development to determine if the changes could directly or indirectly affect the safety or efficacy of the product. These assessments might include both nonclinical studies and clinical trials, 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.

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 updates, 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 the following: (1) product characteristics, (2) seriousness of the condition and medical need, (3) manufacturing processes, (4) the robustness of the sponsor's quality system, and (5) the strength of the sponsor's risk-based quality assessment.

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.

[41] See the guidance for industry *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment* (March 2005) and the draft guidance for industry *FDA's Application of Statutory Factors in Determining When a REMS Is Necessary* (September 2016). When final, this guidance will represent the FDA's current thinking on this topic.

[42] 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.

The need for larger amounts of the drug during later phase trials 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 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 to drug batches (or biological product lots) used in earlier nonclinical studies or clinical trials, then additional nonclinical studies and clinical trials 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. Examples of some of the many ways a change in drug characteristics may adversely affect drug development include the following:

- The amount or type of impurities in a drug product used in clinical trials should be comparable to the drug batches used in toxicology studies. Changes might raise concerns that the drug used in later clinical trials 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 trials might raise concerns that the safety and effectiveness findings of the clinical trials do not apply to the newly manufactured drug. This 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 References for a list of selected guidances).

IX. ADDITIONAL CONSIDERATIONS

A. Participation of Patients, Caregivers, and Advocates

FDA encourages involvement of patients, their caregivers, and advocates in the rare disease drug development process. Their input may provide important information about their experiences, perspectives, needs, and priorities related to potential endpoints and meaningful changes during the review of an investigational drug. Patients can engage and provide input in numerous ways, such as participating in advisory committees, serving as a disease-specific patient representative, contributing to patient-focused drug development initiatives, providing solicited consultation on scientific issues (e.g., clinically meaningful outcome measures), and participating in natural history studies.[43] For drugs in development under an IND, FDA is subject to strict

[43] See the draft guidance for industry, FDA staff, and other stakeholders *Patient-Focused Drug Development: Collecting Comprehensive and Representative Input* (June 2018). When final, this guidance will represent the FDA's current thinking on this topic. For more information, see the Learn About Patient Engagement at the FDA web page available at https://www.fda.gov/ForPatients/PatientEngagement/default.htm#PFDD_2.

confidentiality requirements and may not be able to discuss with the public specific information about a drug development program.[44] 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

Most rare diseases are serious or life-threatening disorders with unmet medical needs and, 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, priority review designation, and accelerated approval. For details on eligibility and applications for expedited program designation, sponsors should consult the guidance for industry *Expedited Programs for Serious Conditions — Drugs and Biologics* (May 2014) and the draft guidance for industry *Expedited Programs for Regenerative Medicine Therapies for Serious Conditions* (November 2017).[45]

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.[46] When preparing development plans, sponsors should consider whether the rare disease affects both children and adults or only children. 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 formulations of the drug to enable accurate dosing, down to the youngest children affected by the rare disease.

For studies in which both pediatric and adult patients 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 patients enrolled in clinical studies beyond those provided for adult patients.[47] These additional safeguards could limit the use of some procedures in children, which

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[44] For example, see 21 CFR 314.430.

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

[46] The regulation governing labeling requirements defines the pediatric population as including patients aged "birth to 16 years, including age groups often called neonates, infants, children, and adolescents." 21 CFR 201.57(c)(i)(iv)(A). For the purposes of pediatric drug development, FDA interprets "birth to 16 years" to mean from birth to before the seventeenth birthday.

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

would otherwise 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 patients in clinical studies.

X. 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.[48] FDA's 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 trial, and whether proposed investigations are likely to produce the data and information needed to meet requirements for a marketing application.[49] FDA provides formal advice through milestone meetings (e.g., pre-IND meeting, end of phase 1 meeting).

FDA can also provide informal support through interactions with FDA staff and offices (e.g., CDER including Rare Diseases Program and Professional Affairs and Stakeholder Engagement, Center for Biologics Evaluation and Research (CBER), Office of Orphan Products Development, Office of the Commissioner (Patient Affairs Staff).

For sponsors seeking early scientific and medical discussion for drug development considerations, FDA has a forum called Critical Path Innovation Meetings (CPIM) in which CDER staff and investigators from industry, academia, patient advocacy groups, and government discuss improving efficiency and success in drug development.[50] In CPIM, CDER staff members often provide general advice on how a technology or methodology might be used to enhance drug development. CBER participates in CPIM meetings when cross-cutting issues arise that involve both centers. In addition, CBER created the Initial Targeted Engagement for Regulatory Advice on CBER Products (INTERACT) meeting program for potential sponsors to engage with CBER staff and obtain advice on a specific topic or issue that is critical to early drug product development. The advice provided by CBER staff to a potential sponsor during an INTERACT meeting may help streamline development by, for example, helping sponsors to avoid unnecessary preclinical studies.

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

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

[50] See the guidance for industry *Critical Path Innovation Meetings* and the FDA Critical Path Innovation Meetings (CPIM) web page at https://www.fda.gov/drugs/developmentapprovalprocess/druginnovation/ucm395888.htm.

REFERENCES[1]

Draft guidances for industry[2]

Adaptive Design Clinical Trials for Drugs and Biologics

Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)

Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products

Expedited Programs for Regenerative Medicine Therapies for Serious Conditions

FDA's Application of Statutory Factors in Determining When a REMS Is Necessary

Human Gene Therapy for Rare Diseases

Investigational Enzyme Replacement Therapy Products: Nonclinical Assessment

Labeling for Human Prescription Drug and Biological Products Approved Under the Accelerated Approval Regulatory Pathway

Rare Diseases: Early Drug Deevelopment and the Role of Pre-IND Meetings

Draft guidance for industry, FDA staff, and other stakeholders[3]

Patient-Focused Drug Development: Collecting Comprehensive and Representative Input

Guidances for FDA reviewers and sponsors

Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Somatic Cell Therapy Investigational New Drug Applications (INDs)

Guidances for industry

CGMP for Phase 1 Investigational Drugs

Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products

[1] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[2] When final, these guidances will represent the FDA's current thinking on these topics. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[3] When final, this guidance will represent the FDA's current thinking on this topics. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Critical Path Innovation Meetings

Determining the Extent of Safety Data Collection Needed in Late-Stage Premarket and Postapproval Clinical Investigations

Expanded Access to Investigational Drugs for Treatment Use — Questions and Answers

Expedited Programs for Serious Conditions—Drugs and Biologics

Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products

Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment

Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims

Potency Tests for Cellular and Gene Therapy Products

Preclinical Assessment of Investigational Cellular and Gene Therapy Products

Premarketing Risk Assessment

Process Validation: General Principles and Practices

Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products

Guidance for industry and FDA staff

Qualification Process for Drug Development Tools

Guidance for industry and review staff

Best Practices for Communication Between IND Sponsors and FDA During Drug Development

ICH guidances for industry

E1A, The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions

E4 Dose-Response Information to Support Drug Registration

E6 Good Clinical Practice: Consolidated Guidance

E8 General Considerations for Clinical Trials

E9 Statistical Principles for Clinical Trials

E10 Choice of Control Group and Related Issues in Clinical Trials

M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals

M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals Questions and Answers (R2)

Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process

Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances

Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products

Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients

Q10 Pharmaceutical Quality System

S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals

S7A Safety Pharmacology Studies for Human Pharmaceuticals

S9 Nonclinical Evaluation for Anticancer Pharmaceuticals

Other resources

FDA, Food and Drug Administration Safety and Innovation Act (FDASIA) Section 1137: Patient Participation in Medical Product Discussions Report on Stakeholder Views, January 2016, https://www.fda.gov/downloads/ForPatients/About/UCM486859.pdf

FDA, Externally Led Patient-Focused Drug Development Meetings, December 2015, https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm453856.htm

FDA, Developing Products for Rare Diseases and Conditions, October 2018, https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/default.htm