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

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Lucas Kempf at 301-796-1140 or (CBER) the Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010.

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

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TABLE OF CONTENTS

Rare Diseases: Early Drug Development and the Role of Pre-IND Meetings 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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 of rare diseases in early development and in the planning of and participation in formal pre-investigational new drug application (pre-IND) meetings with the Food and Drug Administration (FDA).[2] Although also applicable to drug development for common diseases, this guidance is primarily intended to support and facilitate drug development for the treatment of rare diseases.

This guidance describes frequently encountered issues to consider in early drug development and pre-IND meetings including topics related to pharmaceutical quality, nonclinical evaluation, clinical pharmacology, and clinical development including early phase study designs and statistical analysis plans.

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.

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

[2] The term *sponsor* as used in this guidance refers to both industry sponsor as well as sponsor-investigator. The term *drug* as used in this guidance refers to both human drugs and biological products unless otherwise specified.

II. BACKGROUND

Section 526(a)(2)(A) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) defines a rare disease as a disease or condition that affects fewer than 200,000 people in the United States.[3] Early and careful planning is important for all drug development programs but is particularly critical for rare disease drug development for a variety of reasons. The limited number of patients available for the study population affects the feasibility of certain studies, and there is typically a lack of drug development precedent. During drug development, sponsors can request formal meetings with FDA. These meetings may be particularly helpful for sponsors of drugs being developed for rare disease indications. A pre-IND meeting is often the first regulatory communication between the sponsor and FDA regarding the development program for an investigational drug or a new indication for an approved drug. During pre-IND meetings, sponsors can discuss with FDA the unique challenges of rare disease drug development and where regulatory flexibility can be justified.[4]

III. REGULATORY AND SCIENTIFIC CONSIDERATIONS

Issues discussed during pre-IND meetings may vary depending on the drug, program development stage, and targeted disease. However, sponsors should consider the following issues (especially when preparing a pre-IND meeting package) to help FDA reviewers understand the development program and to guide discussion on specific issues. For standard pre-IND meeting package elements, see the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.[5]

A. Pharmaceutical Quality Considerations

Regulations in 21 CFR 312.23(a)(7)(i) emphasize sequential CMC submissions to the IND to support each phase of drug development. These submissions should include information to ensure acceptable quality (e.g., identity, purity, strength/potency) of the investigational drug for the intended phase of the drug development.

[3] Section 526(a)(2)(B) of the FD&C Act 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."

[4] For discussion on pre-IND meetings, procedures for requesting meetings, rescheduling and canceling meetings, content and timing of meeting package submissions, and the conduct and documentation of meetings, see the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants*. See also the guidance for industry and review staff *Best Practices for Communication Between IND Sponsors and FDA During Drug Development* and the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*. When final, this guidance will represent 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.

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

Therefore, at the pre-IND meeting for a rare disease drug development program, the sponsor should clearly summarize the type and amount of CMC information to be submitted in the IND and justify the appropriateness of the information in supporting the proposed clinical trials (e.g., number of patients in the proposed trials, trial durations, and a safety risk assessment).

In addition to providing standard meeting background material,[6] sponsors should include additional detailed information to enable meaningful discussion of the specific questions posed to FDA. The following topics may be appropriate based upon the questions of interest:

- A description of the drug substance, including its physical, chemical, and/or biological characteristics and its source (e.g., synthetic, animal-derived, plant-derived, biotechnology-derived)

- A description of the drug product including dosage form, formulation, and route of administration; if a combination product, a description of the components that comprise the combination product

- A description of the manufacturing processes for the drug substance and drug product and, for a sterile product, a description of the control strategy for assuring the sterility of the product (e.g., aseptic filling methods and controls and/or terminal sterilization method and controls)

- For biologics, a description of the potency assay and its relationship to the mechanism of action and, as applicable, a summary of information on viral clearance studies

- A description of the testing strategy to characterize the drug, including structural, physicochemical, impurity/degradant characterization and release testing strategy

- A description of any differences (e.g., manufacturing process, impurity profiles) between the nonclinical batch(es) and the proposed clinical trial batch(es)

- A description of the container closure systems used for long-term and in-use storage, the procedures for shipping and handling, and the stability testing strategy

- A description of proposed device delivery systems and delivery procedures, as applicable, and the plan to evaluate product compatibility/stability in the intended delivery device

- A listing of the manufacturing facilities used to manufacture clinical lots and, if known, the proposed manufacturing facilities to be used for commercial manufacturing (if different) and a plan for the transition from the clinical manufacturing to the commercial manufacturing facilities

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

B. Nonclinical Considerations

Nonclinical studies provide information used to assess whether conducting human clinical trials with the investigational drug would be reasonably safe.[7] The types of studies needed for an investigational drug depend on the drug's intended use, the proposed clinical trial population (e.g., healthy volunteers versus patients with the indicated disease, anticipated age group), and the proposed treatment regimen. FDA can exercise flexibility in nonclinical programs where the proposed clinical indications are for treatment of rare diseases, particularly diseases that are serious and life threatening.[8]

The ICH guidance for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* provides an overall description of the nonclinical studies generally needed for all drug development programs. The ICH guidance for industry *S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* provides an overall description of the nonclinical studies of biological products that sponsors should consider to support clinical trials. In some cases, an abbreviated or deferred program may be applicable.[9] Pharmacology and toxicology testing in an animal model of disease, when available, may contribute to the overall understanding of the actions of the drug on disease pathology and on the safety profile, especially when drug toxicity may be more severe in the presence of disease pathology.[10] For recommendations on the substance and scope of nonclinical studies to support clinical trials for cell and gene therapy products, refer to the FDA guidance for industry *Preclinical Assessment of Investigational Cellular and Gene Therapy Products*.

In pre-IND meetings, sponsors should be prepared to discuss whether the completed nonclinical studies and the proposed nonclinical study plan for the intended clinical drug formulation are sufficient to support proof of concept and to inform the safety of the drug before initiating first-in-human studies.

In addition to providing the standard meeting package elements,[11] sponsors should include the following information to support specific nonclinical questions posed to the FDA review division/office:

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

[8] See 21 CFR 312.80.

[9] See the ICH guidance for industry *S9 Nonclinical Evaluation for Anticancer Pharmaceuticals.*

[10] We support the principles of the 3Rs (reduce/refine/replace) for animal use in testing when feasible. The FDA encourages sponsors to consult with review divisions when considering a nonanimal testing method 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.

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

- The rationale for the proposed clinical indication, patient population, and clinical dosing plan.

- A description of and rationale for the proposed nonclinical plan to support the initial clinical development strategy, including the selection of appropriate animal models and appropriate species for toxicity evaluation.

- A nonclinical plan that supports the initiation of clinical studies by demonstrating the prospect of direct benefit in any planned pediatric age groups, as applicable. The plan should also include the selection of appropriate animal models and appropriate species for specific pediatric toxicity evaluation, as applicable.

- A summary (not full reports) of completed in vitro and in vivo pharmacology, proof of concept, and toxicology studies.

- A summary of relevant published information on the drug or related drugs, when available, and a summary of safety information for all components of the formulation.

- A description of how toxicities identified from nonclinical studies may be addressed in humans (e.g., modifying the exposure, clinical monitoring, stopping criteria), based on the drug's toxicological profile and safety margins.

FDA may exercise flexibility in the types and amount of nonclinical data to accept to support drug development for serious and life-threatening diseases. In a pre-IND meeting, sponsors can discuss with FDA the additional nonclinical studies that may be necessary to support clinical trials (e.g., chronic toxicity, developmental and reproductive toxicity (DART), carcinogenicity studies) and the timing of those studies, as applicable.

C. Clinical Pharmacology Considerations

Clinical pharmacology studies provide critical information on a drug's mechanism of action, pharmacokinetic and pharmacodynamic properties, potential for clinical benefit, safety profile, and dose- or exposure-response relationship. These studies also enable therapeutic individualization based on assessment of the impact of intrinsic factors (e.g., renal and hepatic function, weight, race, sex, genetics) and extrinsic factors (e.g., concomitant drug use, food intake) on drug response.

Although studies in healthy subjects may determine which factors influence a drug's disposition or pharmacodynamic effects, dedicated clinical trials that inform dosing and usage instructions in the target population with a rare disease may be limited. Therefore, careful planning of the clinical pharmacology aspects of the drug development plan for a rare disease is important, because information from such studies and analyses can inform trial design and serve as supportive evidence of effectiveness. Data generated from such studies and analyses can efficiently optimize conditions for drug use (e.g., dose, schedule, patient selection).

The FDA can exercise flexibility in determining which clinical pharmacology studies are essential to inform the safe and effective use of a drug, whether integrated with clinical efficacy and safety trials or conducted separately in healthy subjects, as well as which clinical pharmacology studies may be deferred until after a drug is approved. Sponsors should be familiar with the expectations for including clinical pharmacology information in a new drug application. See the References section for a list of relevant guidance documents that may be helpful in planning the clinical pharmacology aspects of the drug development program.

In addition to providing the standard meeting package elements[12] and a general overview of the planned human pharmacokinetic evaluation, sponsors should include the following information to address specific clinical pharmacology questions:

- The known or suspected mechanism of action of the drug and its metabolites.

- A summary of nonclinical or clinical study results regarding pharmacokinetic and pharmacodynamic properties of the drug (e.g., in vitro drug metabolism and transport study results). The results should include a discussion of the effect of potential predictors of variability on the drug's pharmacokinetics and pharmacodynamics.

- A justification of the dose selection (e.g., dosing range, number of doses, dose interval, route of administration, pivotal biomarkers) and patient selection strategy (e.g., enrichment), including an assessment of factors that can contribute to variability in a patient's response to the drug. Modeling and simulations approaches can be used to inform the drug's dosing and elements of the trial design.

- Detailed synopses of all proposed studies including planned pharmacokinetic/pharmacodynamic sampling and biomarker assessments that will inform dosing.

- Status of the bioanalytical method validation for all biomarkers.

- Plans for conducting population pharmacokinetic, exposure-response modeling and simulation analyses, particularly for pediatric patients.

- Plans for in vitro diagnostic development, including adherence to regulatory requirements for investigational devices, as applicable.

D. Clinical Considerations

Sponsors developing drugs for rare diseases face many challenges. These may include the small number of disease-affected individuals, lack of understanding of the natural history of the disorder, lack of precedent for drug development (e.g., established clinical endpoints, validated biomarkers), phenotypic heterogeneity, and the need to conduct trials in pediatric populations,

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

among others. Because of the limitations in patient numbers, it is important to maximize the contribution of each patient in the clinical development program. Participants should be randomized from the first patient enrolled in a trial (when feasible) to help ensure interpretable results.

Although FDA has no specified minimum number of patients needed to establish drug safety and efficacy, the number of patients should be adequate to assess benefit and risk. While the approval standard for drugs treating rare diseases is the same as that for drugs treating nonrare diseases, it is appropriate for FDA to exercise the broadest possible scientific judgment in applying the evidentiary standard in the rare disease setting. To that end, FDA will consider: (1) benefits and risks of the drug; (2) seriousness of the disease; and (3) if there is an unmet medical need. This approach reflects FDA's recognition that patients and physicians are generally willing to accept greater risks and side effects from treatment of life-threatening and severely debilitating diseases than they would for other diseases.[13]

It is important that sponsors be prepared to discuss with FDA in pre-IND meetings the following topics:

- A disease description, including prevalence in adult and pediatric patients (including populations outside the United States), availability of patients for clinical trials, disease etiology (including information on genotypic/phenotypic correlation, if the disease is genetic), clinical manifestations, diagnostic criteria, approved therapies and standard of care, rate and pattern of progression, prognosis, variability among patients, and the knowledge gaps in the disease's natural history.

- Description and rationale for the following: proposed clinical trial design(s), efficacy endpoints, biomarkers trial population, patient selection criteria, choice of control group, methods used to minimize bias, overview of statistical analysis plan (including the sample size and power calculation when possible), and statistical analysis methods.

- If the trial population is a subgroup of the population with the rare disease, plans for evaluating the drug in other subgroups to determine whether trial results can be generalized to the broader disease population.

- Anticipated safety issues (based on animal data or pharmacologic properties), plans for monitoring and mitigating such issues (e.g., immunogenicity testing for therapeutic protein products, gene, or cellular products) and ways to augment the safety database if necessary (e.g., using data from drugs in the same class, data from an expanded access program).

- Trial stopping rules and/or criteria for taking the patient off study.

- Plans for an independent data monitoring committee (DMC) to identify and respond to early safety issues. The guidance for clinical trial sponsors *Establishment and Operation*

[13] See 21 CFR 312.80.

of Clinical Trial Data Monitoring Committees discusses the roles, responsibilities, and operating procedures of a DMC and when to use one.

- Inclusion of patient perspectives in the drug development plan

- Plans to conduct extension studies to evaluate longer term safety and durability of effect.

- Considerations related to novel endpoints including the development of clinical outcomes assessments (e.g., patient reported, observer reported, clinician reported, performance outcome measures).[14]

- Plans for pediatric studies, as applicable (see section IV.D., Pediatric Studies).

Sponsors may consider the pros and cons of alternative study designs such as platform studies. Platform studies coordinate with other similar drug development programs for the purpose of sharing placebo patients and study burden.

IV. ADDITIONAL CONSIDERATIONS

A. Expedited Programs for Serious Conditions

A pre-IND meeting is an opportunity for sponsors to consult FDA on how to use the expedited programs for the development and review of investigational drugs. These expedited programs include fast track designation, breakthrough therapy designation, priority review designation, accelerated approval, and regenerative medicine advanced therapy (RMAT) designation. The guidance for industry *Expedited Programs for Serious Conditions — Drugs and Biologics* provides information on FDA's policies, procedures, and criteria generally applicable to most of these programs.[15]

B. Companion Diagnostics

Sponsors often develop drugs for a specific subtype of patients based on particular genetic or molecular features. Drugs in development that are intended to be used in a biomarker-defined subtype of patients may require a companion diagnostic. Companion diagnostics are tests that provide information essential for the safe and effective use of a corresponding drug. Therefore, FDA recommends that sponsors discuss drug diagnostic codevelopment early in the drug development program if the drug is likely to only have a favorable benefit-risk profile in a biomarker-defined subtype of patients.[16]

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

[15] See also the draft guidance for industry on *Expedited Programs for Regenerative Medicine Therapies for Serious Conditions* for information about the RMAT designation program and the application of other expedited programs to regenerative medicine therapies. When final, this guidance will represent the FDA's current thinking on this topic.

[16] See guidance for industry and FDA staff *In Vitro Companion Diagnostic Devices*.

C. Orphan Drug Product Incentives

The Office of Orphan Products Development (OOPD) administers several programs to provide incentives for the development of products (drugs, biologics, devices, or medical foods) for rare diseases or conditions. These programs include Orphan Drug Designation, Rare Pediatric Disease Designation (administered in conjunction with the Office of Pediatric Therapeutics), Humanitarian Use Device Designation, Orphan Products Clinical Trials Grants, Orphan Products Natural History Grants, and Pediatric Device Consortia Grants. During pre-IND meetings for rare disease drug development programs, the sponsor often asks whether the drug is eligible for orphan drug designation for the disease or condition under consideration. Sponsors can submit a formal request for orphan drug designation for their drugs at any time *before* submitting the marketing application for the drug. Other questions related to orphan product development incentives can be discussed at the pre-IND meeting or directly with OOPD.[17]

D. Pediatric Studies

For purposes of drug development, pediatric patients are defined as those patients from birth to 17 years of age, including neonates.[18] Sponsors should include pediatric patients in studies of rare diseases as soon as scientifically and ethically appropriate. Early in drug development, sponsors should discuss with FDA at what point pediatric patients can be included in an overall rare disease product development program. Additionally, sponsors enrolling pediatric patients in any FDA-regulated clinical study must comply with appropriate regulatory and ethical requirements, including the additional safeguards for children.

In studies where the risk to children is more than minimal, drug development studies could be allowed to proceed if the risk is justified by the anticipated benefit to the child and the relation of the anticipated benefit to the risk is at least as favorable as that presented by available alternative approaches.[19] To justify initial studies of rare diseases in children, the sponsor should provide data to establish that pediatric patients are likely to benefit from treatment with the investigational drug (i.e., prospect of direct benefit). Prospect of direct benefit can come from adult data, or in some instances, nonclinical animal disease models can also provide proof of concept that the investigational drug may have a beneficial effect in affected children. Sponsors

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[17] For information on OOPD and its programs, see the OOPD's web page at https://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/officeofscienceandhealthcoordination/ucm2018190.htm.

[18] See 21 CFR 201.57(c)(9)(iv)(A) ("the terms pediatric population(s) and pediatric patient(s) are defined as the pediatric age group, from birth to 16 years, including age groups often called neonates, infants, children, and adolescents") and the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans*. When final, this guidance will represent the FDA's current thinking on this topic. For 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 seventeenth birthday (i.e., birth through 16 years of age).

[19] 21 CFR 50.52.

can consider consultation with experts trained in ethics for programs that involve pediatric patients.

The Pediatric Research Equity Act (PREA), as amended and codified in section 505B of the FD&C Act, requires sponsors of certain new drug applications (NDAs) or biologics license applications (BLAs) and certain supplements to such applications to submit an assessment of the safety and effectiveness of the drug in pediatric patients at the time the application is submitted, unless the requirement has been deferred or waived.[20] An initial pediatric study plan (iPSP) is required to be submitted within 60 days of an end of phase 2 meeting,[21] and an agreed-upon iPSP must be included with submission of an NDA or BLA. However, for serious and life-threatening diseases (including rare diseases), FDA encourages sponsors to submit their plans for pediatric product development as early as feasible before initiating pediatric studies. Some drugs may be exempted from requirements under PREA, such as certain drugs that have orphan drug designation.[22] Nevertheless, FDA encourages sponsors to submit pediatric study plans for all drugs intended for pediatric indications (including drugs exempted from the requirement) to help facilitate pediatric drug development.

E. Data Standards and Electronic Submissions

Sponsors should consult FDA guidances for industry regarding time lines and requirements for providing submissions in electronic format and use of data standards for the submission of applications for INDs, NDAs, and BLAs.[23, 24] Implementation should occur as early as possible during product development so that data standards are accounted for in the design, conduct, and analysis of nonclinical studies and clinical trials.[25]

[20] Section 505B(a)(1) of the FD&C Act. Sponsors of applications to which section 505B (often referred to by the name of the Act that originally created it, PREA) applies must submit either a pediatric assessment or a report on a molecularly targeted pediatric cancer investigation, depending on the application in question.

[21] Section 505B(e)(2)(A) of the FD&C Act (21 U.S.C. 355c(e)(2)(A)). Section 505B(e)(2)(A)(ii)(II) also permits submission of an iPSP at "such other time as may be agreed upon between [FDA] and the applicant."

[22] See section 505B(k) of the FD&C Act (21 U.S.C. 355c(k)).

[23] See guidance for industry *Providing Regulatory Submissions in Electronic Format — Standardized Study Data*.

[24] See section 745A(a) of the FD&C Act (21 U.S.C. 379k-1). See also the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*.

[25] For specifications regarding implementation and submission of nonclinical study and clinical trial data in standardized formats, see the Center for Drug Evaluation and Research web page, Study Data Standards for Submission to CDER, at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

REFERENCES[1]

Formal Meetings

Draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*[2]

Guidance for industry and review staff *Best Practices for Communication Between IND Sponsors and FDA During Drug Development*

Chemistry, Manufacturing, and Controls

Guidance for FDA reviewers and sponsors *Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)*

Guidance 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)*

Guidance for industry *CGMP for Phase 1 Investigational Drugs*

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

Guidance for industry *INDs for Phase 2 and Phase 3 Studies — Chemistry, Manufacturing, and Controls Information*

Guidance for industry, investigators, and reviewers *Exploratory IND Studies*

Nonclinical

Draft guidance for industry *Investigational Enzyme Replacement Therapy Products: Nonclinical Assessment*[3]

Guidance for industry *Preclinical Assessment of Investigational Cellular and Gene Therapy Products*

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

[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, 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.

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

ICH guidance for industry *S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals*

Clinical

Critical Path Innovation Meetings (CPIM) web page at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm395888.htm

Draft guidance for industry *Bioanalytical Method Validation*[4]

Draft guidance for industry *Clinical Drug Interaction Studies — Study Design, Data Analysis, and Clinical Implications*[5]

Draft guidance for industry *Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products*[6]

Draft guidance for industry *Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling*[7]

Draft guidance for industry *Multiple Endpoints in Clinical Trials*[8]

Draft guidance for industry *Rare Diseases: Common Issues in Drug Development*[9]

Draft guidance for industry *Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act*[10]

Guidance for clinical trial sponsors *Establishment and Operation of Clinical Trial Data Monitoring Committees*

Guidance for industry and FDA staff *In Vitro Companion Diagnostic Devices*

Guidance for industry and staff *Qualification Process for Drug Development Tools*

Guidance for industry *Codevelopment of Two or More New Investigational Drugs for Use in Combination*

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

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

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

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

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

Guidance for industry *Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products*

Guidance for industry *Expedited Programs for Serious Conditions — Drugs and Biologics*

Guidance for industry *Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications*

Guidance for industry *Gene Therapy Clinical Trials — Observing Subjects for Delayed Adverse Events*

Guidance for industry *Non-Inferiority Clinical Trials to Establish Effectiveness*

Guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*

Guidance for industry *Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*

Guidance for industry *Population Pharmacokinetics*

Guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*

ICH guidance for industry *E8 General Considerations for Clinical Trials*

ICH guidance for industry *E9 Statistical Principles for Clinical Trials*

ICH guidance for industry *E10 Choice of Control Group and Related Issues in Clinical Trials*

ICH guidance for industry *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs*

ICH guidance for industry *E16 Biomarkers Related to Drug or Biotechnology Product Development: Context, Structure, and Format of Qualification Submissions*

Roadmap to Patient-Focused Outcome Measurement in Clinical Trials web page at https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/UCM370174.pdf

Orphan Product Development

Designating Humanitarian Use Device web page at https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/DesignatingHumanitarianUseDevicesHUDS/default.htm

Designating an Orphan Product: Drugs and Biological Products web page at https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/default.htm

Office of Orphan Products Development web page at https://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/officeofscienceandhealthcoordination/ucm2018190.htm

Orphan Products Clinical Trials Grants Program web page at https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/WhomtoContactaboutOrphanProductDevelopment/default.htm

Orphan Products Natural History Grants Program web page at https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/OrphanProductsNaturalHistoryGrantsProgram/default.htm

Pediatric Device Consortia Grant Program web page at https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/PediatricDeviceConsortiaGrantsProgram/default.htm

Rare Pediatric Disease Priority Review Voucher Program web page at https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/RarePediatricDiseasePriorityVoucherProgram/default.htm

Pediatric

Draft guidance for industry *General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products*[11]

Draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans*[12]

Pediatric Device Consortia Grant Program web page at https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/PediatricDeviceConsortiaGrantsProgram/default.htm

Data Standards

Guidance for industry *Providing Regulatory Submissions in Electronic Format — Standardized Study Data*

Study Data Standards for Submission to CDER web page at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

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

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

Investigational New Drug Applications

Investigational new drug application web navigational tool (with links to guidances for industry, FDA forms, and online references), available on the Investigator-Initiated Investigational New Drug (IND) Applications web page at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm343349.htm

Office of Cellular, Tissue, and Gene Therapies (OCTGT) webinar series (multiple presentations on regulatory information for sponsors planning to submit an IND to the Center for Biologics Evaluation and Research for an investigational cell therapy or gene therapy product), available on the OTAT (Office of Tissues and Advanced Therapies) Learn web page at https://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm