

# Guidance Documents for Rare Disease Drug Development

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.

Below are selected guidances that are relevant to rare disease drug development, organized by topic. This list does not include all FDA guidances on or relevant to rare disease drug development but represents our most commonly used guidances. This list may be updated periodically.

You can search all FDA Guidances by topic, FDA Center, or issue date [here](#) ([/regulatory-information/search-fda-guidance-documents](#)).

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## Rare Disease

## Rare Diseases: Natural History Studies for Drug Development: Draft Guidance for Industry (</regulatory-information/search-fda-guidance-documents/rare-diseases-natural-history-studies-drug-development>)

FDA is publishing this draft guidance to help inform the design and implementation of natural history studies that can be used to support the development of safe and effective drugs and biological products for rare diseases. A natural history study collects information about the natural history of a disease in the absence of an intervention, from the disease's onset until either its resolution or the individual's death. Although knowledge of a disease's natural history can benefit drug development for many disorders and conditions, natural history information is usually not available or is incomplete for most rare diseases; therefore, natural history information is particularly needed for these diseases.

## Rare Diseases: Common Issues in Drug Development Guidance for Industry (</regulatory-information/search-fda-guidance-documents/rare-diseases-common-issues-drug-development-guidance-industry>)

This guidance assists sponsors of drug and biological products intended to treat or prevent rare diseases in conducting more efficient and successful development programs through a discussion of selected issues commonly encountered in rare disease drug development.

## Rare Diseases: Early Drug Development and the Role of Pre-IND Meetings : Draft Guidance for Industry (</regulatory-information/search-fda-guidance-documents/rare-diseases-early-drug-development-and-role-pre-ind-meetings>)

The purpose of this draft guidance is to assist sponsors of drug and biological products for the treatment of rare diseases in planning and conducting more efficient and productive pre-investigational new drug application (pre-IND) meetings. Drug development for rare diseases has many challenges related to the nature of these diseases. This draft guidance is intended to advance and facilitate the development of drugs and biological products for the treatment of rare diseases.

## Rare Pediatric Disease Priority Review Vouchers (</regulatory-information/search-fda-guidance-documents/rare-pediatric-disease-priority-review-vouchers>)

This guidance provides information on the implementation of section 908 of the Food and Drug Administration Safety and Innovation Act (FDASIA), which added section 529 to the Federal Food, Drug, and Cosmetic Act (the FD&C Act). Under section 529, FDA will award priority review vouchers to sponsors of certain rare pediatric disease product applications that meet the criteria specified in that section.

## Rare Diseases: Early Drug Development and the Role of Pre-IND Meetings : Draft Guidance for Industry (</regulatory-information/search-fda-guidance-documents/rare-diseases-early-drug-development-and-role-pre-ind-meetings>)

The purpose of this draft guidance is to assist sponsors of drug and biological products for the treatment of rare diseases in planning and conducting more efficient and productive pre-

investigational new drug application (pre-IND) meetings. Drug development for rare diseases has many challenges related to the nature of these diseases. This draft guidance is intended to advance and facilitate the development of drugs and biological products for the treatment of rare diseases.

[Slowly Progressive, Low-Prevalence Rare Diseases with Substrate Deposition That Results from Single Enzyme Defects: Providing Evidence of Effectiveness for Replacement or Corrective Therapies : Guidance for Industry](#) (/regulatory-information/search-fda-guidance-documents/slowly-progressive-low-prevalence-rare-diseases-substrate-deposition-results-single-enzyme-defects)

This document provides guidance to sponsors on the evidence necessary to demonstrate the effectiveness of investigational new drugs or new drug uses intended for slowly progressive, low-prevalence rare diseases that are associated with substrate deposition and are caused by single enzyme defects. This guidance applies only to those low-prevalence rare diseases with well-characterized pathophysiology, and in which changes in substrate deposition can be readily measured in relevant tissue or tissues.

[Pediatric Rare Diseases--A Collaborative Approach for Drug Development Using Gaucher Disease as a Model : Draft Guidance for Industry](#) (/regulatory-information/search-fda-guidance-documents/pediatric-rare-diseases-collaborative-approach-drug-development-using-gaucher-disease-model-draft)

The purpose of this guidance is to facilitate drug development in pediatric rare diseases. In particular, it discusses a new possible approach to enhance the efficiency of drug development in pediatric rare diseases using Gaucher disease as an example.

[Inborn Errors of Metabolism That Use Dietary Management: Considerations for Optimizing and Standardizing Diet in Clinical Trials for Drug Product Development: Guidance for Industry](#) (/regulatory-information/search-fda-guidance-documents/inborn-errors-metabolism-use-dietary-management-considerations-optimizing-and-standardizing-diet)

This guidance describes the Food and Drug Administration's (FDA's) current recommendations regarding how to optimize and standardize dietary management in clinical trials for the development of drugs that treat inborn errors of metabolism (IEM) for which dietary management is a key component of patients' metabolic control. Optimizing dietary management in these patients before entry into and during clinical trials is essential to providing an accurate evaluation of the efficacy of new drug products.

## **Benefit-Risk**

[Benefit-Risk Assessment for New Drug and Biological Products](#) (/regulatory-information/search-fda-guidance-documents/benefit-risk-assessment-new-drug-and-biological-products)

The intent of this guidance is to clarify for drug sponsors and other stakeholders how

considerations about a drug's benefits, risks, and risk management options factor into certain premarket and postmarket regulatory decisions that the Food and Drug Administration (FDA or Agency) makes about new drug applications (NDAs) submitted under section 505(c) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) as well as biologics license applications (BLAs) submitted under section 351(a) of the Public Health Service Act (PHS Act).

## Biomarkers

For general information on Biomarkers, please see [About Biomarkers and Qualification \(/drugs/biomarker-qualification-program/about-biomarkers-and-qualification\)](#).

[Biomarker Qualification: Evidentiary Framework \(/regulatory-information/search-fda-guidance-documents/biomarker-qualification-evidentiary-framework\)](#).

This draft guidance provides recommendations on general considerations to address when developing a biomarker for qualification under the 21st Century Cures Act (Cures Act), enacted on December 13, 2016, that added a new section to the Federal Food, Drug, and Cosmetic Act (FD&C Act). Qualification of a biomarker is a determination that within the stated context of use, the biomarker can be relied on to have a specific interpretation and application in drug development and regulatory review.

[Qualification Process for Drug Development Tools \(/regulatory-information/search-fda-guidance-documents/qualification-process-drug-development-tools-guidance-industry-and-fda-staff\)](#)

This guidance describes the qualification process for drug development tools (DDTs) intended for potential use, over time, in multiple drug development programs.

## Clinical Pharmacology

[Bioavailability Studies Submitted in NDAs or INDs – General Considerations \(/regulatory-information/search-fda-guidance-documents/bioavailability-studies-submitted-ndas-or-inds-general-considerations\)](#)

This guidance provides recommendations to sponsors and applicants submitting bioavailability (BA) information for drug products in investigational new drug applications (INDs), new drug applications (NDAs), and NDA supplements. This guidance contains recommendations on how to meet the BA requirements set forth in 21 CFR part 320 as they apply to dosage forms intended for oral administration.

[General Clinical Pharmacology Considerations for Pediatric Studies of Drugs, Including Biological Products \(/regulatory-information/search-fda-guidance-documents/general-clinical-pharmacology-considerations-pediatric-studies-drugs-including-biological-products\)](#)

This guidance assists sponsors of investigational new drug applications (INDs) and applicants of new drug applications (NDAs) under section 505 of the Federal Food, Drug, and Cosmetic Act

(the FD&C Act), biologics license applications (BLAs) under section 351(a) of the Public Health Service Act (PHS Act), and supplements to such applications who are planning to conduct clinical studies in pediatric populations.

[General Clinical Pharmacology Considerations for Neonatal Studies for Drugs and Biological Products Guidance for Industry \(/regulatory-information/search-fda-guidance-documents/general-clinical-pharmacology-considerations-neonatal-studies-drugs-and-biological-products-guidance\)](#)

This guidance is intended to assist sponsors of investigational new drug applications (INDs) and applicants of new drug applications (NDAs), biologics license applications (BLAs), and supplements to such applications who are planning to conduct clinical studies in neonatal populations. This guidance provides recommendations for neonatal clinical pharmacology studies, whether the studies are conducted pursuant to section 505A of the Federal Food, Drug, and Cosmetic Act (FD&C Act), section 505B of the FD&C Act, or neither.

[Assessing the Effects of Food on Drugs in INDs and NDAs – Clinical Pharmacology Considerations \(/regulatory-information/search-fda-guidance-documents/assessing-effects-food-drugs-inds-and-ndas-clinical-pharmacology-considerations\)](#)

This guidance provides recommendations to sponsors planning to conduct food-effect (FE) studies for orally administered drug products under investigational new drug applications (INDs) to support new drug applications (NDAs) and supplements to these applications for drugs being developed under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355).

[Population Pharmacokinetics \(/regulatory-information/search-fda-guidance-documents/population-pharmacokinetics\)](#)

This guidance is intended to assist sponsors and applicants of new drug applications (NDAs), biologics license applications (BLAs), abbreviated new drug applications (ANDAs), and investigational new drugs (IND) applications in the application of population pharmacokinetic (PK) analysis.

[Clinical Pharmacology Considerations for Antibody-Drug Conjugates Guidance for Industry \(/regulatory-information/search-fda-guidance-documents/clinical-pharmacology-considerations-antibody-drug-conjugates-guidance-industry\)](#)

This guidance provides recommendations to assist industry and other parties involved in the development of antibody-drug conjugates (ADCs) with a cytotoxic small molecule drug or payload. Specifically, this guidance addresses the FDA's current thinking regarding clinical pharmacology considerations and recommendations for ADC development programs, including bioanalytical methods, dosing strategies, dose- and exposure-response analysis, intrinsic factors, QTc assessments, immunogenicity, and drug-drug interactions (DDIs).

## Drug-Drug Interaction Assessment for Therapeutic Proteins Guidance for Industry

(</regulatory-information/search-fda-guidance-documents/drug-drug-interaction-assessment-therapeutic-proteins-guidance-industry>).

The purpose of this guidance is to help sponsors of investigational new drug applications (INDs) and applicants of biologic license applications (BLAs) determine the need for drug-drug interaction (DDI) studies for a therapeutic protein (TP) by providing a systematic, risk-based approach.

## Developing Targeted Therapies in Low-Frequency Molecular Subsets of a Disease (</regulatory-information/search-fda-guidance-documents/developing-targeted-therapies-low-frequency-molecular-subsets-disease>)

The pharmacological effect of a targeted therapy is often related to a particular molecular alteration, and many diseases are caused by a range of different molecular alterations (some of which may be rare). Therefore, a targeted therapy may have differential effects among patients with the same disease who have different molecular alterations. The purpose of this guidance is to describe general approaches to evaluating the benefits and risks of targeted therapeutics within a clinically defined disease where some molecular alterations may occur at low frequencies.

## Clinical Pharmacogenomics: Premarket Evaluation in Early-Phase Clinical Studies and Recommendations for Labeling (</regulatory-information/search-fda-guidance-documents/clinical-pharmacogenomics-premarket-evaluation-early-phase-clinical-studies-and-recommendations>)

This guidance is intended to assist the pharmaceutical industry and other investigators engaged in new drug development in evaluating how variations in the human genome, specifically DNA sequence variants, could affect a drug's pharmacokinetics (PK), pharmacodynamics (PD), efficacy, or safety. The guidance provides recommendations on when and how genomic information should be considered to address questions arising during drug development and regulatory review.

## **Clinical Trials**

All clinical trials guidances are listed [here](#) (</regulatory-information/search-fda-guidance-documents/clinical-trials-guidance-documents>).

## E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) (</regulatory-information/search-fda-guidance-documents/e6r2-good-clinical-practice-integrated-addendum-ich-e6r1>)

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human

subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

**E8(R1) General Considerations for Clinical Studies** (</regulatory-information/search-fda-guidance-documents/e8r1-general-considerations-clinical-studies>)

This guidance describes internationally accepted principles and practices in the design and conduct of clinical studies of drug and biological products. The guidance is intended to assist sponsors and other parties that design clinical studies, and to promote the quality of the studies submitted to regulatory authorities, while allowing for flexibility.

**Multiple Endpoints in Clinical Trials Guidance for Industry** (</regulatory-information/search-fda-guidance-documents/multiple-endpoints-clinical-trials-guidance-industry>)

The purpose of this guidance is to describe various strategies for grouping and ordering endpoints for analysis and applying some well-recognized statistical methods for managing multiplicity within a study in order to control the chance of making erroneous conclusions about a drug's effects. Basing a conclusion on an analysis where the risk of false conclusions has not been appropriately controlled can lead to false or misleading representations regarding a drug's effects.

**Diversity Plans to Improve Enrollment of Participants From Underrepresented Racial and Ethnic Populations in Clinical Trials: Draft Guidance for Industry** (</regulatory-information/search-fda-guidance-documents/diversity-plans-improve-enrollment-participants-underrepresented-racial-and-ethnic-populations>)

The purpose of this guidance is to provide recommendations to sponsors developing medical products on the approach for developing a Race and Ethnicity Diversity Plan (referred to as the "Plan") to enroll adequate numbers of participants in clinical trials from underrepresented racial and ethnic populations in the United States.

**E17 General Principles for Planning and Design of Multi-Regional Clinical Trial** (</regulatory-information/search-fda-guidance-documents/e17-general-principles-planning-and-design-multi-regional-clinical-trials>)

With the increasing globalization of drug development, it has become important that data from multiregional clinical trials (MRCTs) can be accepted by regulatory authorities across regions and countries as the primary source of evidence to support marketing approval of drugs (medicinal products). The purpose of this guidance is to describe general principles for the planning and design of MRCTs with the aim of increasing the acceptability of MRCTs in global regulatory submissions.

**Decentralized Clinical Trials for Drugs, Biological Products, and Devices** (</regulatory-information/search-fda-guidance-documents/decentralized-clinical-trials-drugs-biological-products-and-devices>)

This draft guidance provides recommendations for sponsors, investigators, and other stakeholders regarding the implementation of decentralized clinical trials (DCTs) for drugs, biological products, and devices. In this guidance, a DCT refers to a clinical trial where some or all of the trial-related activities occur at locations other than traditional clinical trial sites.

[Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products: Guidance for Industry](#) (/regulatory-information/search-fda-guidance-documents/enrichment-strategies-clinical-trials-support-approval-human-drugs-and-biological-products)

The purpose of this guidance is to assist industry in developing enrichment strategies that can be used in clinical investigations intended to demonstrate effectiveness (and in some cases safety) of human drugs and biological products. This guidance defines several types of enrichment strategies, provides examples of potential clinical trial designs, and discusses potential regulatory considerations when using enrichment strategies in clinical trials.

[Ethical Considerations for Clinical Investigations of Medical Products Involving Children](#) (/regulatory-information/search-fda-guidance-documents/ethical-considerations-clinical-investigations-medical-products-involving-children)

Clinical investigations in children are essential for obtaining data on the safety and effectiveness of drugs, biological products, and medical devices in children and to protect children from the risks associated with exposure to medical products that may be unsafe or ineffective. Children are a vulnerable population who cannot consent for themselves and who therefore are afforded additional safeguards when participating in a clinical investigation. Such safeguards are an essential requirement for the initiation and conduct of pediatric investigations as part of a medical product development program.

## **Complex Innovative Trial Design**

[Adaptive Design Clinical Trials for Drugs and Biologics Guidance for Industry](#) (/regulatory-information/search-fda-guidance-documents/adaptive-design-clinical-trials-drugs-and-biologics-guidance-industry).

This document provides guidance to sponsors and applicants submitting investigational new drug applications (INDs), new drug applications (NDAs), biologics licensing applications (BLAs), or supplemental applications on the appropriate use of adaptive designs for clinical trials to provide evidence of the effectiveness and safety of a drug or biologic. The guidance describes important principles for designing, conducting, and reporting the results from an adaptive clinical trial. The guidance also advises sponsors on the types of information to submit to facilitate FDA evaluation of clinical trials with adaptive designs, including Bayesian adaptive and complex trials that rely on computer simulations for their design.

## [Interacting with FDA on Complex Innovative Trial Designs for Drugs and Biological Products \(/regulatory-information/search-fda-guidance-documents/interacting-fda-complex-innovative-trial-designs-drugs-and-biological-products\)](#)

This document provides guidance to sponsors and applicants on interacting with the FDA on complex innovative trial design (CID) proposals for drugs or biological products. This guidance discusses the use of novel trial designs in the development and regulatory review of drugs and biological products, how sponsors may obtain feedback on technical issues related to modeling and simulation, and the types of quantitative and qualitative information that should be submitted for review.

## **Communication with FDA**

### [Best Practices for Communication Between IND Sponsors and FDA Drug Development \(/regulatory-information/search-fda-guidance-documents/best-practices-communication-between-ind-sponsors-and-fda-during-drug-development\)](#)

This guidance describes best practices and procedures for timely, transparent, and effective communications between investigational new drug application (IND) sponsors and FDA at critical junctures in drug development, which may facilitate earlier availability of safe and effective drugs to the American public.

## **Digital Health**

### [Use of Electronic Health Record Data in Clinical Investigations Guidance for Industry \(/regulatory-information/search-fda-guidance-documents/use-electronic-health-record-data-clinical-investigations-guidance-industry\)](#)

This guidance is intended to assist sponsors, clinical investigators, contract research organizations, institutional review boards (IRBs), and other interested parties on the use of electronic health record data in FDA-regulated clinical investigations.

### [Digital Health Technologies for Remote Data Acquisition in Clinical Investigations \(/regulatory-information/search-fda-guidance-documents/digital-health-technologies-remote-data-acquisition-clinical-investigations\)](#)

This guidance provides recommendations to sponsors, investigators, and other stakeholders on the use of digital health technologies (DHTs) to acquire data remotely from participants in clinical investigations evaluating medical products. DHTs may take the form of hardware and/or software and may be used to gather health-related information from study participants and transmit that information to study investigators and/or other authorized parties to evaluate the safety and effectiveness of medical products.

## **Effectiveness**

[Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products](#)  
(/regulatory-information/search-fda-guidance-documents/providing-clinical-evidence-effectiveness-human-drug-and-biological-products)

This guidance is intended to provide guidance to sponsors planning to file NDAs, BLAs or supplemental applications to demonstrate effectiveness. May 1998.

[Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products](#)  
(/regulatory-information/search-fda-guidance-documents/demonstrating-substantial-evidence-effectiveness-human-drug-and-biological-products)

This document is intended to provide guidance to applicants planning to file new drug applications (NDAs), biologics license applications (BLAs), or applications for supplemental indications on the evidence to be provided to demonstrate effectiveness. This guidance complements and expands on the 1998 guidance entitled Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (the 1998 guidance).

## **Expanded Access**

[Expanded Access to Investigational Drugs for Treatment Use - Questions and Answers](#)  
(/regulatory-information/search-fda-guidance-documents/expanded-access-investigational-drugs-treatment-use-questions-and-answers)

This guidance provides information for industry, researchers, physicians, institutional review boards (IRBs), and patients about the implementation of FDA's regulations on expanded access to investigational drugs for treatment use under an investigational new drug application (IND) (21 CFR part 312, subpart I), which went into effect on October 13, 2009.

[Individual Patient Expanded Access Applications: Form FDA 3926](#) (/regulatory-information/search-fda-guidance-documents/individual-patient-expanded-access-applications-form-fda-3926)

This guidance describes Form FDA 3926 (Individual Patient Expanded Access - Investigational New Drug Application (IND)), which is available for licensed physicians to use for expanded access requests for individual patient INDs. The terms compassionate use and preapproval access are also occasionally used in the context of the use of an investigational drug to treat a patient; however, these terms are not defined or described in FDA regulations. Individual patient expanded access allows for the use of an investigational new drug<sup>3</sup> outside of a clinical investigation, or the use of an approved drug where availability is limited by a risk evaluation and mitigation strategy (REMS), for an individual patient who has a serious or immediately life-threatening disease or condition and there is no comparable or satisfactory alternative therapy for submitting an IND under 21 CFR 312.23 for use in cases of individual patient expanded access, including for emergency use.

## **Expedited Programs**

## [Expedited Programs for Serious Conditions - Drugs and Biologics \(/regulatory-information/search-fda-guidance-documents/expedited-programs-serious-conditions-drugs-and-biologics\)](#)

The following four FDA programs are intended to facilitate and expedite development and review of new drugs to address unmet medical need in the treatment of a serious or life-threatening condition: fast track designation, breakthrough therapy designation, accelerated approval, and priority review designation.

## **Individualized Antisense Oligonucleotide Drugs Products**

### [Draft Guidance: IND Submissions for Individualized Antisense Oligonucleotide Drug Products for Severely Debilitating or Life-Threatening Diseases: Clinical Recommendations \(/regulatory-information/search-fda-guidance-documents/ind-submissions-individualized-antisense-oligonucleotide-drug-products-severely-debilitating-or-life\)](#)

This guidance is intended for sponsor-investigators (hereafter referred to as sponsors) developing individualized investigational antisense oligonucleotide (ASO) drug products for a severely debilitating or life-threatening (SDLT) genetic disease. Most often, individuals with such diseases will have no alternative treatment options, and their diseases will be rapidly progressing, resulting in early death and/or devastating or irreversible morbidity within a short time frame without treatment. In these situations, drug development targeted to a larger number of patients with the same disease is not anticipated because of the specificity of the mechanism of action of the ASO combined with the rarity of the treatment-amenable patient population. The gene variant or variants that are targeted by the ASO drug product should be unique to the trial participant(s) and generally only reported in a small number of patients (typically 1 to 2) in the disease population.

### [Draft Guidance: IND Submissions for Individualized Antisense Oligonucleotide Drug Products for Severely Debilitating or Life-Threatening Diseases: Chemistry, Manufacturing, and Controls Recommendations \(/regulatory-information/search-fda-guidance-documents/investigational-new-drug-application-submissions-individualized-antisense-oligonucleotide-drug\)](#)

The purpose of this guidance is to provide recommendations regarding the chemistry, manufacturing, and controls (CMC) information that should be provided in an investigational new drug application (IND) submitted by a sponsor-investigator (hereafter referred to as sponsor) developing an individualized antisense oligonucleotide (ASO) drug product for a severely debilitating or life-threatening (SDLT) disease caused by a unique genetic variant where only a small number of individuals are prospectively identified (typically one or two). These individualized ASO drug products should be from a well-characterized chemical class for which there is substantial clinical and nonclinical experience that is either publicly available or to which the sponsor has a right to reference.

Draft Guidance: IND Submissions for Individualized Antisense Oligonucleotide Drug Products: Administrative and Procedural Recommendations Guidance for Sponsor-Investigators  
[\(/regulatory-information/search-fda-guidance-documents/ind-submissions-individualized-antisense-oligonucleotide-drug-products-administrative-and-procedural\)](/regulatory-information/search-fda-guidance-documents/ind-submissions-individualized-antisense-oligonucleotide-drug-products-administrative-and-procedural).

The focus of this guidance is on administrative and procedural aspects of interacting with FDA on development programs for individualized ASO drug products, such as the approach to obtaining feedback from FDA and the expectations and process for making regulatory submissions to FDA.

Draft Guidance: Nonclinical Testing of Individualized Antisense Oligonucleotide Drug Products for Severely Debilitating or Life-Threatening Diseases Guidance for Sponsor-Investigators  
[\(/regulatory-information/search-fda-guidance-documents/nonclinical-testing-individualized-antisense-oligonucleotide-drug-products-severely-debilitating-or\)](/regulatory-information/search-fda-guidance-documents/nonclinical-testing-individualized-antisense-oligonucleotide-drug-products-severely-debilitating-or).

The purpose of this guidance is to describe the nonclinical information that FDA recommends to support an investigational new drug application (IND) for an antisense oligonucleotide being developed to treat a severely debilitating or life-threatening (SDLT) disease caused by a unique genetic variant where only a small number of individuals are prospectively identified (usually one or two).

## **Investigational New Drug Applications**

Investigational New Drug Applications Prepared and Submitted by Sponsor-Investigators  
[\(/regulatory-information/search-fda-guidance-documents/investigational-new-drug-applications-prepared-and-submitted-sponsor-investigators\)](/regulatory-information/search-fda-guidance-documents/investigational-new-drug-applications-prepared-and-submitted-sponsor-investigators).

The purpose of this guidance is to assist sponsor-investigators in preparing and submitting complete investigational new drug applications (INDs) to the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration (FDA). Sponsor-investigators seeking to do clinical research often do not have the regulatory knowledge or the resources to hire experts to help them with the IND submission process. Although not an exhaustive step-by-step instruction manual, this guidance highlights certain elements of this process to facilitate a sponsor-investigator's successful submission of an IND.

Investigational New Drug Applications (INDs) - Determining Whether Human Research Studies Can Be Conducted Without an IND  
[\(/regulatory-information/search-fda-guidance-documents/investigational-new-drug-applications-inds-determining-whether-human-research-studies-can-be\)](/regulatory-information/search-fda-guidance-documents/investigational-new-drug-applications-inds-determining-whether-human-research-studies-can-be)

This guidance is intended to assist clinical investigators, sponsors, sponsor-investigators, and institutional review boards (IRBs) in determining whether research studies involving human subjects must be conducted under an investigational new drug application (IND), as described in title 21 of the Code of Federal Regulations, part 312 (21 CFR part 312) (the IND regulations).

This guidance describes when an IND is required, specific situations in which an IND is not required, and a range of issues that, in FDA's experience, have been the source of confusion or misperceptions about the application of the IND regulations.

**IND Submissions for Individualized Antisense Oligonucleotide Drug Products for Severely Debilitating or Life-Threatening Diseases: Clinical Recommendations** ([/regulatory-information/search-fda-guidance-documents/ind-submissions-individualized-antisense-oligonucleotide-drug-products-severely-debilitating-or-life](#))

This guidance is intended for sponsor-investigators (hereafter referred to as sponsors) developing individualized investigational antisense oligonucleotide (ASO) drug products for a severely debilitating or life-threatening (SDLT) genetic disease. Most often, individuals with such diseases will have no alternative treatment options, and their diseases will be rapidly progressing, resulting in early death and/or devastating or irreversible morbidity within a short time frame without treatment. In these situations, drug development targeted to a larger number of patients with the same disease is not anticipated because of the specificity of the mechanism of action of the ASO combined with the rarity of the treatment-amenable patient population.

## **Meetings with FDA**

**Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products** ([/regulatory-information/search-fda-guidance-documents/formal-meetings-between-fda-and-sponsors-or-applicants-pdufa-products-guidance-industry](#))

This guidance provides recommendations to industry on formal meetings between the Food and Drug Administration (FDA) and sponsors or applicants relating to the development and review of drug or biological drug products.

**Best Practices for Communication Between IND Sponsors and FDA Drug Development** ([/regulatory-information/search-fda-guidance-documents/best-practices-communication-between-ind-sponsors-and-fda-during-drug-development](#))

This guidance describes best practices and procedures for timely, transparent, and effective communications between investigational new drug application (IND) sponsors and FDA at critical junctures in drug development, which may facilitate earlier availability of safe and effective drugs to the American public.

**Rare Diseases: Early Drug Development and the Role of Pre-IND Meetings : Draft Guidance for Industry** ([/regulatory-information/search-fda-guidance-documents/rare-diseases-early-drug-development-and-role-pre-ind-meetings](#))

The purpose of this draft guidance is to assist sponsors of drug and biological products for the treatment of rare diseases in planning and conducting more efficient and productive pre-investigational new drug application (pre-IND) meetings. Drug development for rare diseases

has many challenges related to the nature of these diseases. This draft guidance is intended to advance and facilitate the development of drugs and biological products for the treatment of rare diseases.

[Meetings with the Office of Orphan Products Development \(/regulatory-information/search-fda-guidance-documents/meetings-office-orphan-products-development\)](#)

This guidance provides recommendations to industry, researchers, patient groups, and other stakeholders (collectively referred to in this guidance as “stakeholders”) interested in requesting a meeting, including a teleconference, with the Food and Drug Administration’s (FDA’s) Office of Orphan Products Development (OOPD) on issues related to orphan-drug designation requests, humanitarian use device (HUD) designation requests, rare pediatric disease designation requests, funding opportunities through the Orphan Products Grants Program and the Pediatric Device Consortia Grants Program, and orphan product patient-related topics of concern.

## New Drug Applications (NDAs)

For a list of Guidances on how to prepare an NDA submission, please see the [New Drug Application \(NDA\) \(/drugs/types-applications/new-drug-application-nda\)](#) webpage.

[Benefit-Risk Assessment for New Drug and Biological Products \(/regulatory-information/search-fda-guidance-documents/benefit-risk-assessment-new-drug-and-biological-products\)](#)

The intent of this guidance is to clarify for drug sponsors and other stakeholders how considerations about a drug’s benefits, risks, and risk management options factor into certain premarket and postmarket regulatory decisions that the Food and Drug Administration (FDA or Agency) makes about new drug applications (NDAs) submitted under section 505(c) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) as well as biologics license applications (BLAs) submitted under section 351(a) of the Public Health Service Act (PHS Act).

## Neurology

[Amyotrophic Lateral Sclerosis: Developing Drugs for Treatment Guidance for Industry \(/regulatory-information/search-fda-guidance-documents/amyotrophic-lateral-sclerosis-developing-drugs-treatment-guidance-industry\)](#)

The purpose of this guidance is to assist sponsors in the clinical development of drugs and biological products for the treatment of amyotrophic lateral sclerosis (ALS). Specifically, this guidance addresses the Food and Drug Administration’s (FDA’s) current thinking regarding the clinical development program and clinical trial designs for drugs to support an indication for the treatment of ALS.

[Considerations for Long-Term Clinical Neurodevelopmental Safety Studies in Neonatal Product Development](/regulatory-information/search-fda-guidance-documents/considerations-long-term-clinical-neurodevelopmental-safety-studies-neonatal-product-development)

The purpose of this guidance is to provide a framework for considering whether and what type of long-term neurologic, sensory and developmental evaluations could be useful to support a determination of safety of a drug, biological product, or device (referred to as ‘medical product’ in this guidance) for use in neonates, and if so, which domains of neurodevelopment may be most applicable.

[Duchenne Muscular Dystrophy and Related Dystrophinopathies: Developing Drugs for Treatment Guidance for Industry](/regulatory-information/search-fda-guidance-documents/duchenne-muscular-dystrophy-and-related-dystrophinopathies-developing-drugs-treatment-guidance)

This guidance addresses FDA’s current thinking regarding clinical development programs and trial designs for drugs to support an indication for the treatment of one or more dystrophinopathies: Duchenne muscular dystrophy (DMD) and related dystrophinopathies including Becker muscular dystrophy (BMD), DMD-associated dilated cardiomyopathy (DCM), and symptomatic carrier states in females. The most prominent pathology in dystrophinopathies is degeneration of skeletal and cardiac muscle leading to progressive loss of muscle function, respiratory and cardiac failure, and premature death.

## **Non-Clinical**

[M3\(R2\) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals](/regulatory-information/search-fda-guidance-documents/m3r2-nonclinical-safety-studies-conduct-human-clinical-trials-and-marketing-authorization)

The purpose of this document is to recommend international standards for, and promote harmonization of, the nonclinical safety studies recommended to support human clinical trials of a given scope and duration as well as marketing authorization for pharmaceuticals.

[Nonclinical Safety Evaluation of the Immunotoxic Potential of Drugs and Biologics Guidance for Industry](/regulatory-information/search-fda-guidance-documents/nonclinical-evaluation-immunotoxic-potential-pharmaceuticals)

The purpose of this guidance is to assist sponsors in their nonclinical evaluation of the immunotoxic potential of drugs and biologics by supplementing the recommendations on nonclinical immune system assessments provided across the following guidance documents:

- International Council for Harmonisation (ICH) guidances for industry:
- S8 Immunotoxicity Studies for Human Pharmaceuticals (April 2006)
- 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 (May 2012)
- S5(R3) Detection of Toxicity to Reproduction for Human Pharmaceuticals (November 2017)

### [Investigational Enzyme Replacement Therapy Products: Nonclinical Assessment \(/regulatory-information/search-fda-guidance-documents/investigational-enzyme-replacement-therapy-products-nonclinical-assessment\)](#)

The purpose of this guidance is to help sponsors design and conduct nonclinical studies during development of investigational enzyme replacement therapy (ERT) products. Specifically, this guidance describes the Food and Drug Administration's (FDA's) current thinking about the substance and scope of nonclinical information needed to support initiation of clinical trials, ongoing clinical development, and marketing approval for investigational ERT products.

### **Orphan Designation**

### [Clarification of Orphan Designation of Drugs and Biologics for Pediatric Subpopulations of Common Diseases \(/regulatory-information/search-fda-guidance-documents/clarification-orphan-designation-drugs-and-biologics-pediatric-subpopulations-common-diseases\)](#)

This guidance is intended for sponsors of drugs and biological products (hereafter drugs1) who are considering submitting requests for orphan-drug designation for their drugs under section 526 of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

### **Patient Focused Drug Development (PFDD)**

### [Patient-Focused Drug Development: Collecting Comprehensive and Representative Input \(/regulatory-information/search-fda-guidance-documents/patient-focused-drug-development-collecting-comprehensive-and-representative-input\)](#)

This guidance (Guidance 1) is the first of a series of four methodological patient-focused drug development (PFDD) guidance documents that FDA is developing to address, in a stepwise manner, how stakeholders (patients, researchers, medical product developers and others) can collect and submit patient experience data and other relevant information from patients and caregivers for medical product development and regulatory decision making.

### [Patient-Focused Drug Development: Methods to Identify What Is Important to Patients \(/regulatory-information/search-fda-guidance-documents/patient-focused-drug-development-methods-identify-what-important-patients\)](#)

This guidance (Guidance 2) is the second in a series of four methodological patient-focused drug development (PFDD) guidance documents that FDA is developing to describe in a stepwise manner how stakeholders (patients, researchers, medical product developers and others) can collect and submit patient experience data and other relevant information from patients and caregivers to be used for medical product development and regulatory decision-making.

[Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments \(/regulatory-information/search-fda-guidance-documents/patient-focused-drug-development-selecting-developing-or-modifying-fit-for-purpose-clinical-outcome\)](#)

This guidance (Guidance 3) is the third in a series of four methodological patient-focused drug development (PFDD) guidance documents that describe how stakeholders (patients, caregivers, researchers, medical product developers, and others) can collect and submit patient experience data and other relevant information from patients and caregivers to be used for medical product development and regulatory decision-making.

[Patient-Focused Drug Development: Incorporating Clinical Outcome Assessments Into Endpoints for Regulatory Decision-Making \(/regulatory-information/search-fda-guidance-documents/patient-focused-drug-development-incorporating-clinical-outcome-assessments-endpoints-regulatory\)](#)

This guidance (Guidance 4) is the fourth in a series of four methodological patient-focused drug development (PFDD) guidance documents that describe how stakeholders (patients, caregivers, researchers, medical product developers, and others) can collect and submit patient experience data and other relevant information from patients and caregivers to be used for medical product development and regulatory decision-making.

## Patient Reported Outcomes

[Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims \(/regulatory-information/search-fda-guidance-documents/patient-reported-outcome-measures-use-medical-product-development-support-labeling-claims\)](#)

This guidance describes how the Food and Drug Administration (FDA) reviews and evaluates existing, modified, or newly created patient-reported outcome (PRO) instruments used to support claims in approved medical product labeling. A PRO instrument (i.e., a questionnaire plus the information and documentation that support its use) is a means to capture PRO data used to measure treatment benefit or risk in medical product clinical trials.

## Pediatrics

[Ethical Considerations for Clinical Investigations of Medical Products Involving Children \(/regulatory-information/search-fda-guidance-documents/ethical-considerations-clinical-investigations-medical-products-involving-children\)](#)

Clinical investigations in children are essential for obtaining data on the safety and effectiveness of drugs, biological products, and medical devices in children and to protect children from the risks associated with exposure to medical products that may be unsafe or ineffective. Children are a vulnerable population who cannot consent for themselves and who therefore are afforded

additional safeguards when participating in a clinical investigation. Such safeguards are an essential requirement for the initiation and conduct of pediatric investigations as part of a medical product development program.

**E11(R1) Addendum: Clinical Investigation of Medicinal Products in the Pediatric Population**  
[\(/regulatory-information/search-fda-guidance-documents/e11r1-addendum-clinical-investigation-medicinal-products-pediatric-population\)](/regulatory-information/search-fda-guidance-documents/e11r1-addendum-clinical-investigation-medicinal-products-pediatric-population)

Pediatric drug development has evolved since the original guidance E11 Clinical Investigation of Medicinal Products in the Pediatric Population (ICH E11 (2000)) published, requiring consideration of regulatory and scientific advances relevant to pediatric populations. This addendum does not alter the scope of the original guidance. ICH E11 (2000), including this addendum (R1); is not intended to be comprehensive; other ICH guidances, as well as documents from regulatory authorities worldwide, the World Health Organization (WHO), and pediatric societies, provide additional detail. The purpose of the addendum is to complement and provide clarification and current regulatory perspective on topics in pediatric drug development.

## **Real World Evidence**

**Use of Electronic Health Records in Clinical Investigations**  
[\(/regulatory-information/search-fda-guidance-documents/use-electronic-health-record-data-clinical-investigations-guidance-industry\)](/regulatory-information/search-fda-guidance-documents/use-electronic-health-record-data-clinical-investigations-guidance-industry)

This guidance is intended to assist sponsors, clinical investigators, contract research organizations, institutional review boards (IRBs), and other interested parties on the use of electronic health record data in FDA-regulated clinical investigations.

**Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products**  
[\(/regulatory-information/search-fda-guidance-documents/real-world-data-assessing-electronic-health-records-and-medical-claims-data-support-regulatory\)](/regulatory-information/search-fda-guidance-documents/real-world-data-assessing-electronic-health-records-and-medical-claims-data-support-regulatory)

This draft guidance is intended to provide sponsors, researchers, and other interested stakeholders with considerations when proposing to use electronic health records or medical claims data in clinical studies to support a regulatory decision for effectiveness or safety.

**Data Standards for Drug and Biological Production Submissions Containing Real-World Data**  
[\(/regulatory-information/search-fda-guidance-documents/data-standards-drug-and-biological-product-submissions-containing-real-world-data\)](/regulatory-information/search-fda-guidance-documents/data-standards-drug-and-biological-product-submissions-containing-real-world-data)

This guidance provides recommendations to sponsors for complying with section 745A(a) of the FD&C Act (21 U.S.C. 379k-1(a)) when submitting RWD as study data in applicable drug submissions.

[Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products](#) (/regulatory-information/search-fda-guidance-documents/real-world-data-assessing-registries-support-regulatory-decision-making-drug-and-biological-products). This guidance provides sponsors and other stakeholders with considerations when either proposing to design a registry or using an existing registry to support regulatory decision-making about a drug's effectiveness or safety.

[Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products](#) (/regulatory-information/search-fda-guidance-documents/considerations-use-real-world-data-and-real-world-evidence-support-regulatory-decision-making-drug)

This guidance provides information about the use of RWE to help support approval of a new indication for a drug already approved under section 505(c) of the FD&C Act or to help support postapproval study requirements.

[Submitting Documents Utilizing Real-World Data and Real-World Evidence to FDA for Drugs and Biologics](#) (/regulatory-information/search-fda-guidance-documents/submitting-documents-using-real-world-data-and-real-world-evidence-fda-drug-and-biological-products).

This guidance applies to submissions for investigational new drug applications (INDs), new drug applications (NDAs), and biologics license applications (BLAs) that contain RWD/RWE intended to support a regulatory decision regarding product safety and/or effectiveness.

[Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products](#) (/regulatory-information/search-fda-guidance-documents/considerations-design-and-conduct-externally-controlled-trials-drug-and-biological-products).

This guidance provides recommendations to sponsors and investigators considering the use of externally controlled clinical trials to provide evidence of the safety and effectiveness of a drug product. In an externally controlled trial, outcomes in participants receiving the test treatment according to a protocol are compared to outcomes in a group of people external to the trial who had not received the same treatment. The external control arm can be a group of people, treated or untreated, from an earlier time (historical control), or it can be a group of people, treated or untreated, during the same time period (concurrent control) but in another setting.

[Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices](#) (/regulatory-information/search-fda-guidance-documents/use-real-world-evidence-support-regulatory-decision-making-medical-devices)

FDA is issuing this guidance to clarify how we evaluate real-world data to determine whether they are sufficient for generating the types of real-world evidence that can be used in FDA regulatory decision-making for medical devices.

## Statistical Analysis

## E9 Statistical Principles for Clinical Trials (/regulatory-information/search-fda-guidance-documents/e9-statistical-principles-clinical-trials)

The efficacy and safety of medicinal products should be demonstrated by clinical trials that follow the guidance in E6 Good Clinical Practice: Consolidated Guidance adopted by the ICH, May 1, 1996. The role of statistics in clinical trial design and analysis is acknowledged as essential in that ICH guidance. The proliferation of statistical research in the area of clinical trials coupled with the critical role of clinical research in the drug approval process and health care in general necessitate a succinct document on statistical issues related to clinical trials.

## E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials (/regulatory-information/search-fda-guidance-documents/e9r1-statistical-principles-clinical-trials-addendum-estimands-and-sensitivity-analysis-clinical)

To properly inform decision-making by pharmaceutical companies, regulators, patients, physicians, and other stakeholders, clear descriptions of the benefits and risks of a treatment (medicine) for a given medical condition should be made available. Without such clarity, there is a concern that the reported treatment effect will be misunderstood. This addendum presents a structured framework to strengthen the dialogue between disciplines involved in the formulation of clinical trial objectives, design, conduct, analysis and interpretation, as well as between sponsor and regulator regarding the treatment effect or effects of interest that a clinical trial should address.

## Adjusting for Covariates in Randomized Clinical Trials for Drugs and Biological Products (/regulatory-information/search-fda-guidance-documents/adjusting-covariates-randomized-clinical-trials-drugs-and-biological-products)

This guidance describes FDA's current recommendations regarding adjusting for covariates in the statistical analysis of randomized clinical trials in drug development programs. This guidance provides recommendations for the use of covariates in the analysis of randomized, parallel group clinical trials that are applicable to both superiority trials and noninferiority trials. The main focus of the guidance is on the use of prognostic baseline covariates to improve statistical efficiency for estimating and testing treatment effects.

## **Voucher Program**

### Rare Pediatric Disease Priority Review Vouchers (/regulatory-information/search-fda-guidance-documents/rare-pediatric-disease-priority-review-vouchers)

This guidance provides information on the implementation of section 908 of the Food and Drug Administration Safety and Innovation Act (FDASIA), which added section 529 to the Federal Food, Drug, and Cosmetic Act (the FD&C Act). Under section 529, FDA will award priority review vouchers to sponsors of certain rare pediatric disease product applications that meet the criteria specified in that section.