Learning and Education to ADvance and Empower Rare Disease Drug Developers (LEADER 3D)

Case Study User Guide

I. Introduction

This user guide contains information integral to CDER-regulated drug and biologic product development for rare diseases, such as regulations and how FDA interprets them. By providing an overview of the case studies' structure, plus key concepts, regulatory considerations, and additional resources, this guide will help the rare disease drug development community understand successful approaches from previous drug development programs.

Drug development is challenging, and even more so for rare diseases due to unique challenges (e.g., small patient populations which can limit study design options; diseases with high unmet medical needs that are progressive and life-limiting; phenotypic and genotypic heterogeneity within a condition, a lack of drug development tools). The LEADER 3D case studies are intended to share approaches used by several sponsors when designing and conducting their rare disease drug development programs for drugs and biological products regulated by CDER. By pairing select topics with case examples that incorporate challenges, and potential solutions, these case studies may help navigate the challenges of rare disease drug development.

If involved in the design and conduct of rare disease clinical trials, use this guide and the accompanying case studies to build regulatory knowledge and an understanding of how working with FDA early and throughout the rare disease drug development process is the recommended approach.

Please note the case studies are not intended or designed to provide specific strategies for obtaining product approval. Rare disease drug development is not one-size-fits-all. The kind and quantity of data in each rare disease application will be different based on the unique considerations of each development program and therefore must be assessed on a case-by-case basis.

How to Navigate the LEADER 3D Case Studies

Every case study begins with an overview, including an introduction to the drug, the rare disease or condition, and the drug mechanism of action. The subsequent sections address at least one regulatory topic and include excerpts from relevant FDA guidance documents to increase knowledge and provide insights on FDA's recommended approaches.

A complete list of LEADER 3D case studies and a summary of the regulatory topics addressed are found in Appendix B of this user guide.

We encourage reading the case studies in their entirety to obtain an understanding of fundamental concepts and the considerations that facilitated FDA approval.

Though case study sections may be read in any order, we strongly recommend starting with the sections that introduce the drug, the drug's mechanism of action, and the rare disease or condition to build a comprehensive understanding of the regulatory insights.

Note: The term *drug* refers to both human and biological products regulated by CDER unless otherwise specified.

II. Using the Case Study Materials

Each case study provides supplementary materials to enhance the learning experiences and help apply certain considerations to drug development programs. The supplementary materials include:

- **Figures and Graphics:** These are visual representations of the data provided in the public integrated review document for the drug featured in the case study. Review these to provide additional visualization of regulatory considerations during drug review.
- **FDA Guidance Documents:** These are resources describing FDA recommendations on a particular topic. Reference these documents to guide rare disease drug development work.
- **Additional Resources:** These resources include articles, reports, and other publications that provide more information on specific topics or contexts relevant to each case study.

Supplementary materials can be accessed by clicking on the hyperlinks embedded in the case study text. A list of supplementary materials can also be found in the Additional Resources (Appendix A) at the end of this user guide.

III. Key Concepts and Regulatory Considerations from the Case Studies

Ensuring the regulatory fitness of a rare disease drug development program is critical in the development of rare disease drugs. The case studies presented outline specific approaches that resulted in applications containing fit-for-purpose data and that produced interpretable results.

When designing a rare disease drug development program, one should keep in mind the following key concepts and regulatory considerations. *Please also keep in mind that in addition to demonstrating substantial evidence of effectiveness, there are other important considerations which impact the approval decision, such as whether a drug is safe for its intended use.*

Safety Evaluation

Evaluating whether a drug is safe involves weighing whether the benefits of the drug outweigh its risks under the conditions of use described in labeling. Ultimately, what is a feasible and sufficient safety assessment is a matter of scientific and regulatory judgment based on the particular challenges posed by each drug and disease, including patients' tolerance and acceptance of risk in the setting of unmet medical need and the benefit offered by the drug.

FDA recognizes that when a drug is developed to treat serious diseases for which there are few or no approved therapies, greater uncertainty or greater risks may be acceptable, provided that the substantial evidence standard has been met (substantial evidence is discussed below). More information on clinical safety evaluation can be found in FDA's guidance for industry *Rare Diseases: Considerations for the Development of Drugs and Biological Products* (December 2023).

Demonstrating Substantial Evidence

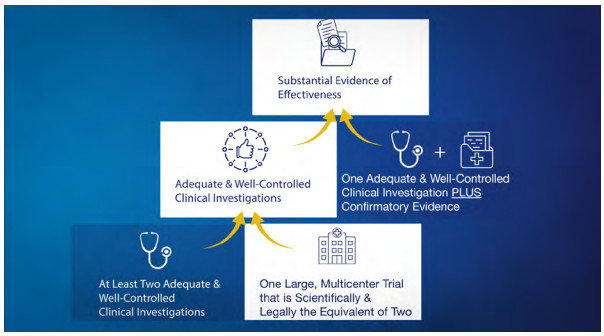
Two Adequate and Well-Controlled Clinical Investigations

To be approved for marketing, a drug must be **safe** and **effective** for its intended use. Under section 505(d) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) a drug's effectiveness must be established by "substantial evidence," which is defined as: "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and reasonably be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof."[1] Reflecting the importance of independent substantiation of experimental results, FDA generally requires at least two adequate and well-controlled clinical investigations, each convincing on its own, to establish effectiveness. FDA regulations at 21 CFR 314.126(b) outline the characteristics of adequate and well-controlled studies.

One Adequate and Well-Controlled Clinical Investigation Plus Confirmatory Evidence

Although, as noted above, FDA generally requires two adequate and well-controlled investigations to meet the "substantial evidence" standard, section 505(d) of the FD&C Act permits FDA to determine, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence, are sufficient to demonstrate substantial evidence of effectiveness (Figure 1). Examples and types of confirmatory evidence can be found in the FDA's draft guidance *Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence* (September 2023)

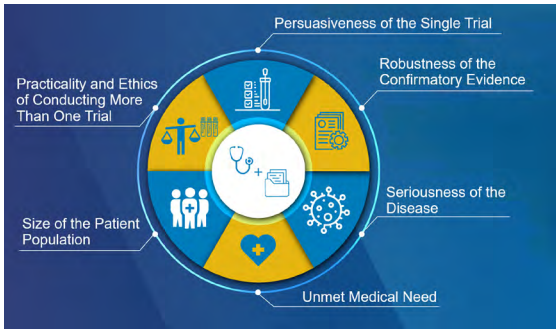
Figure 1: Demonstrating Substantial Evidence of Effectiveness



[1] Section 505(d) of the FD&C Act (21 U.S.C. 355(d)); see also 21 CFR 514.4(a) ("Substantial evidence means evidence consisting of one or more adequate and well-controlled studies, such as a study in a target species, study in laboratory animals, field study, bioequivalence study, or an in vitro study, on the basis of which it could fairly and reasonably be concluded by experts qualified by scientific training and experience to evaluate the effectiveness of the new animal drug involved that the new animal drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof. Substantial evidence shall include such adequate and well-controlled studies that are, as a matter of sound scientific judgment, necessary to establish that a new animal drug will have its intended effect.")

which, when final, will represent the Agency's current thinking on this subject. FDA considers a number of factors when determining if a single adequate and well-controlled clinical investigation plus confirmatory evidence approach meets the substantial evidence of effectiveness standard (Figure 2). These include the persuasiveness of the single trial, the robustness of the confirmatory evidence, the seriousness of the disease, the unmet medical need, the size of the patient population, and the practicality and ethics of conducting more than one trial. The one adequate and well-controlled clinical investigation plus confirmatory evidence approach is frequently used in rare disease drug development.

Figure 2: Examples of Factors Considered to Determine the Substantial Evidence Standard



Clinical Trial Design Features

Randomized, double-blinded, concurrently controlled trials are usually regarded as the "gold standard" to demonstrate effectiveness, since these trials may provide more reliable evidence of a treatment effect compared to other designs. However, FDA recognizes that certain design features may be appropriate when the disease is rare with a high unmet need. For example, drug developers may assign more participants to receive the test drug than the control, or they may conduct a dose comparison design to increase the number of participants receiving the investigational drug. In some circumstances, drug developers may also use crossover, randomized withdrawal, randomized delayed start designs, or a single-arm trial with an external control. Importantly, the suitability of using an external control is informed by several factors and warrants a case-by-case assessment. Rare disease drug development is most successful when it is a collaborative effort, and the recommended approach is to work with FDA early in the process.

Endpoint Selection

For many rare diseases, efficacy endpoints are novel or without precedent for a given condition. Endpoint selection for a clinical trial depends on (1) the range and course of clinical manifestations, (2) clinical characteristics of specific target populations, (3) disease aspects that are meaningful to the patients and caregivers, including disease burden, and (4) the expected effect of the drug being tested. When selecting endpoints, also consider, the validity, sensitivity, reliability, and interpretability of the endpoint as they may be different for patients with mild, early-stage, or slowly progressive forms of a disease compared to patients with severe, late-stage, or rapidly progressive forms of the same disease.

In other words, endpoints must be "fit-for-purpose." The best approach is to work with FDA early in the rare disease drug development process. More information on the development of clinical outcome assessments (COA)- or biomarker- based endpoints, including guidance documents and other resources, can be found in the Additional Resources section below.

Natural History Studies

There is limited knowledge of the natural history for many rare diseases; however, a natural history study can be helpful for planning drug development. Information obtained from a natural history study can play an important role at every stage of drug development, from discovery to the design of clinical studies intended to support marketing approval of a drug (e.g., identification or development of COAs, identification or development of biomarkers, design of externally controlled studies, identification of patient populations), and beyond into the post-marketing period. When collecting natural history data, all the potential uses of the data should be considered, as data collected for one purpose may not be fit-for-use for another purpose. Before using natural history data in a study intended to support regulatory decision-making by FDA, drug developers should consider whether the data are fit-for-use by assessing the data's relevance and reliability. Relevance includes the availability of data for key study variables (such as exposures, outcomes, covariates) and sufficient numbers of representative patients for the study. Reliability refers to accuracy, completeness, and traceability. Drug developers should consult with FDA regarding the appropriateness of using natural history data intended to provide evidence in support of a regulatory decision by FDA.

Dose Selection

Another important feature of rare disease trial design is dose selection, and generally the effects of more than one dose should be studied. Given the limited number of patients, multiple data sources (e.g., data from animal models of disease for different doses, a range of exposure response, intrapatient dose escalation studies, physiologically based pharmacokinetic or pharmacokinetic/pharmacodynamic modeling) should be used to select the dose for safety and efficacy trials.[2] In addition, rare disease drug developers could consider using crossover or seamless phase two-three designs, including those with parallel groups, for dose optimization and efficacy assessments in the same trial.[3] Integrated analyses of all data from other clinical studies or "model-informed" approaches can also aid in dose selection.[2]

IV. Meeting with FDA

These case studies are intended to aid in the consideration of rare disease drug development concepts that might be relevant to a development program. **Collaborative rare disease drug development is the most successful drug development strategy, and the recommended approach is to work with FDA early in the process — before designing clinical trials — to achieve the goal of developing new therapies in the most efficient manner.**

Meetings between drug developers and the Agency are useful in resolving questions and issues raised during drug development. For earlier stages of development, FDA offers several types of meetings including:

- **Critical Path Innovation Meeting (CPIM)**: A means by which CDER and investigators from industry, academia, scientific consortia, patient advocacy groups, and government can communicate to improve efficiency and success in drug development. The goals of the CPIM are to discuss a methodology or technology proposed by the meeting requester and for CDER to provide general advice on how this methodology or technology might enhance drug development. The CPIM does not substitute for formal pre-IND (Pre-Investigational New Drug), IND (Investigational New Drug), NDA (New Drug Application), BLA (Biologics License Application), or other regulatory meetings. CPIM discussions are non-regulatory, drug product-independent and nonbinding on both FDA and CPIM requesters.
- **INitial Targeted Engagement for Regulatory Advice on CBER/CDER ProducTs (INTERACT)**: Meetings intended for novel products and development programs that present unique challenges in early development (i.e., before filing of an IND or before having a pre-IND meeting). These meetings are intended to facilitate IND-enabling efforts when a sponsor is facing novel, challenging issues that might otherwise delay progress toward entering a clinical program.
- **Pre-Investigational New Drug Application (Pre-IND)**: An opportunity to discuss various issues related to considerations for pharmaceutical quality, nonclinical evaluation, clinical pharmacology, and clinical considerations/ challenges for an investigational therapy.

Supplemental information can be found in the Additional Resources section below and on the Accelerating Rare Disease Cures (ARC) website.

V. Appendix

A. Additional Resources

The LEADER 3D Case Study User Guide and case studies contain a variety of key concepts and terms relevant to the drug development process. Some of these may be familiar, while others may be new, but understanding these concepts and terms is an important aspect of drug development. Selected FDA resources that address these concepts and that support rare disease drug development are listed below.

[2] Wang, L, J Wang, J Feng, M Doi, S Pepe, M Pacanowski, and RN Schuck, 2022, Dose-Finding Studies in Drug Development for Rare Genetic Diseases, Orphanet Journal of Rare Diseases, 17(1)

[3] Guidance for industry *Rare Diseases: Considerations for the Development of Drugs and Biologics* (December 2023)

1. Programs Relevant to Rare Disease Drug Development

Accelerating Rare Disease Cures (ARC) Program: Managed by the Center for Drug Evaluation and Research (CDER's) Rare Diseases Team, the ARC Program brings together CDER's collective expertise to provide strategic overview and coordination of CDER's rare disease activities. Those involved in the design and conduct of rare disease clinical trials will find many helpful resources relevant to rare disease drug development on the ARC Program website, including:

- An easily accessible list of relevant guidance documents organized by topic.
- Funding Opportunities for Rare Diseases at FDA.
- Links to **recordings of past meetings and workshops**[4] relevant to rare disease drug development.

Rare Disease Endpoint Advancement (RDEA) Pilot Program: The RDEA Pilot Program is a joint program with CDER and the Center for Biologics Evaluation and Research (CBER). The program is designed to:

- Advance rare disease drug development programs by providing a mechanism for sponsors to collaborate with FDA throughout the efficacy endpoint development process.
- Promote innovation and evolving science by sharing learnings on novel endpoint development through FDA presentations, guidance documents, public workshops, and a public-facing website.

Complex Innovative Trial Design (CID) Meeting Program: The CID Meeting Program was established to support the goal of facilitating and advancing the use of complex adaptive, Bayesian, and other novel clinical trial designs. This paired meeting program offers sponsors whose meeting requests are granted the opportunity for increased interaction with FDA staff to discuss their proposed CID approach.

Model-Informed Drug Development (MIDD) Paired Meeting Program: The MIDD Paired Meeting Program affords sponsors who are selected for participation the opportunity to meet with Agency staff to discuss MIDD approaches in medical product development. The MIDD Paired Meeting Program is designed to provide:

- An opportunity for drug developers and FDA to discuss the application of MIDD approaches to the development and regulatory evaluation of medical products.
- Advice about how particular MIDD approaches can be used in a specific drug development program.

Advancing Real-World Evidence (RWE) Program: The Advancing RWE Program provides sponsors who are selected the opportunity to meet with Agency staff — before protocol development or study initiation — to discuss the use of RWE in medical product development. The Advancing RWE Program is an optional pathway for sponsors submitting RWE proposals.

The Drug Development Tool Qualification Programs: Drug Development Tools (DDTs) are methods, materials, or measures that have the potential to facilitate drug development. Examples of DDTs may include but are not limited to:

- Biomarkers used for clinical trial enrichment
- COAs used to evaluate clinical benefit
- Animal models used for efficacy testing

Biomarker Qualification Program: The mission of the CDER Biomarker Qualification Program (BQP) is to work with external stakeholders to develop biomarkers as drug development tools. Qualified biomarkers have the potential to advance public health by encouraging efficiencies and innovation in drug development.

Clinical Outcome Assessment (COA) Qualification Program: The CDER COA Qualification Program:

- Manages the qualification process for COAs intended to address unmet public health needs.
- Works directly with requestors in guiding COA development for qualification.

[4] See the Upcoming and Recent Events drop down menu on the ARC Program webpage

- Encourages a collaborative, multidisciplinary setting where CDER can review COAs and provide advice on the development or modification of COAs outside the IND/New Drug Application (NDA)/Biologics License Application (BLA) pathway.

Guidance Snapshot Pilot Program: Guidance Snapshots are a communication tool that provide highlights from guidance documents using visuals, podcasts, and plain language. This pilot program is intended to increase general public awareness of and engagement with FDA guidance documents on innovative topics to support the efficient application of the guidance documents' recommendations.

2. Select Guidance Documents[5]

Substantial Evidence of Effectiveness

- Draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological* (December 2019). When final, this guidance will reflect the Agency's current thinking on this topic.
- Draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence* (September 2023). When final, this guidance will reflect the Agency's current thinking on this topic.

Rare Diseases

- Guidance for industry *Rare Diseases: Considerations for the Development of Drugs and Biological Products* (December 2023).
- Draft guidance for industry *Rare Diseases: Natural History Studies for Drug Development* (March 2019). When final, this guidance will reflect the Agency's current thinking on this topic.

Externally Controlled Trials

- Draft guidance for industry *Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products* (February 2023). When final, this guidance will reflect the Agency's current thinking on this topic.

Formal Meetings with FDA

- Guidance for industry *Critical Path Innovation Meetings* (April 2015).
- Draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (September 2023). When final, this guidance will reflect the Agency's current thinking on this topic.
- Draft guidance for industry *Rare Diseases: Early Drug Development and the Role of Pre-IND Meetings* (October 2018). When final, this guidance will reflect the Agency's current thinking on this topic.

Real-World Data and Real-World Evidence

- Guidance for industry *Considerations for the Use of Real-World Data and Real-World Evidence To Support Regulatory Decision-Making for Drug and Biological Products* (August 2023).
- Guidance for industry *Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products* (December 2023).
- Guidance for industry *Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products* (July 2024).

Patient-Focused Drug Development Guidance Series

- Guidance for industry, Food and Drug Administration Staff, and other stakeholders *Patient-Focused Drug Development: Collecting Comprehensive and Representative Input* (June 2018).
- Guidance for industry, Food and Drug Administration staff, and other stakeholders *Patient-Focused Drug Development: Methods to Identify What Is Important to Patients* (February 2022).

[5] For the most recent versions of guidance documents, please see the FDA guidance web page: https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

- Draft guidance for industry, Food and Drug Administration staff, and other stakeholders *Selecting, Developing or Modifying Fit-for-Purpose Clinical Outcomes Assessments* (June 2022). When final, this guidance will reflect the Agency's current thinking on this topic.
- Draft guidance for industry, Food and Drug Administration staff, and other stakeholders *Incorporating Clinical Outcome Assessments into Endpoints for Regulatory Decision Making* (April 2023). When final, this guidance will reflect the Agency's current thinking on this topic.

3. Other Resources

- Biomarkers, Endpoints, and other Tools (BEST) Resource
- FDA Glossary of Terms
- CDER Small Business & Industry Assistance (SBIA): A Comprehensive Resource for Information on Human Drug Development in Regulation

B. LEADER 3D Case Studies

1. **Fosdenopterin (Nulibry) The use of a Single Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence to Demonstrate Substantial Evidence of Effectiveness for a Rare Disease:** In this case study, the Applicant proposed using a single adequate and well-controlled investigation and two types of confirmatory evidence to meet the standard for substantial evidence of effectiveness in the setting of a limited patient population with a rare disease. The Sponsor engaged with the Agency early and throughout their development plan, and submitted the data to support the approval of fosdenopterin as a treatment for molybdenum cofactor deficiency (MoCD) type A.

2. **Olipudase Alfa-rpcp (Xenpozyme) A Clinical Dose Escalation Strategy for a Rare Disease Drug Development Program:** In this case study, the Applicant needed to generate sufficient data in early phase studies to inform dose selection for later phase studies and dose optimization for clinical use due to the limited number of patients with acid sphingomyelinase deficiency (ASMD). To overcome this challenge, the Applicant leveraged multiple data sources for dosing information, including animal studies and clinically relevant biomarkers, to execute a dose-finding clinical investigation to support the approval of olipudase alfa-rpcp for the treatment of ASMD.

3. **Odevixibat (Bylvay) Developing Novel Clinical Outcome Assessment Instruments for Use in the Demonstration of Substantial Evidence of Effectiveness for a Rare Disease:** This case study examines the development and use of clinical outcome assessments (COAs) in the new drug application for odevixibat (Bylvay) for the treatment of pruritus in progressive familial intrahepatic cholestasis (PFIC). For this trial, the Applicant developed two novel COAs using input from the patient community to demonstrate the efficacy of odevixibat. Treatment with odevixibat demonstrated statistically persuasive and clinically meaningful results in improvement of pruritus.

4. **Vutrisiran (Amvuttra) Use of an External Control with a Single Adequate and Well-Controlled Investigation and Confirmatory Evidence to Demonstrate Substantial Evidence of Effectiveness:** In this case study, the Applicant used an external placebo control arm from the study conducted for the approval of patisiran, an already approved therapy for the same indication and with the same mechanism of action. The Applicant established the efficacy of vutrisiran for treating hereditary transthyretin-mediated amyloidosis-polyneuropathy based on positive results from a single adequate and well-controlled investigation that utilized the external placebo control arm. Moreover, the Applicant provided confirmatory evidence from data that offered strong mechanistic support for vutrisiran, as well as mechanistic data and scientific knowledge about the effectiveness of patisiran, which is in the same pharmacological class as vutrisiran.

5. **Tofersen (Qalsody) Use of a Surrogate Endpoint to Demonstrate Substantial Evidence of Effectiveness for an Accelerated Approval:** In this case study, the Applicant discussed with FDA the use of a prognostic biomarker as a surrogate endpoint reasonably likely to predict clinical benefit for the accelerated approval of a drug for a serious rare disease with no available therapies. The FDA evaluated several factors, including mechanistic evidence, the biomarker's prognostic value, its correlation with clinical outcomes, disease seriousness, and lack of available treatments, to conclude that neurofilament light chain (NfL) was an acceptable surrogate endpoint for the accelerated approval of tofersen for SOD1-ALS. The Applicant demonstrated a large, robust, and convincing effect of tofersen on NfL, providing demonstration of an effect on a surrogate endpoint or intermediate clinical endpoint to support accelerated approval.

6. **Avalglucosidase alfa-ngpt (Nexviazyme) and Seladelpar (Livdelzi) Use of Biomarkers as Surrogate Endpoints for Approval:** This case study examines the use of biomarkers as a component of demonstrating substantial evidence of effectiveness to support FDA drug approvals. In the case of avalglucosidase alfa-ngpt (Nexviazyme), the Applicant used a biomarker as a validated surrogate endpoint for traditional approval. In the case of seladelpar (Livdelzi), the Applicant used biomarkers in a composite biochemical endpoint as a surrogate endpoint reasonably likely to predict clinical benefit for accelerated approval.

C. Case Study User Guide References by Order of Appearance

Page 1

- See the FDA Drug Development Tools (DDTs) webpage available at https://www.fda.gov/drugs/development-approval-process-drugs/drug-development-tools-ddts.

Page 2

- See guidance for industry *Rare Diseases: Considerations for the Development of Drugs and Biological Products* (December 2023) for important considerations in rare disease drug and biologics development, available at https://www.fda.gov/media/119757/download.
- See 21 CFR 314.126(b) for more information on the characteristics of adequate and well-controlled studies available at https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-314/subpart-D/section-314.126.
- See draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence* (September 2023) available at https://www.fda.gov/media/172166/download. When final, this guidance will reflect the Agency's current thinking on this topic.
- See 21 CFR 514.4(a) for more information on substantial evidence available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=514.4#:~:text=Substantial%20evidence%20means%20evidence%20consisting,concluded%20by%20experts%20qualified%20by.

Page 4

- See the FDA Accelerating Rare Disease Cures (ARC) webpage available at https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/accelerating-rare-disease-cures-arc-program.
- See Wang, L, J Wang, J Feng, M Doi, S Pepe, M Pacanowski, and RN Schuck, 2022, Dose-Finding Studies in Drug Development for Rare Genetic Diseases, Orphanet Journal of Rare Diseases, 17(1) available at https://ojrd.biomedcentral.com/articles/10.1186/s13023-022-02298-6.
- See guidance for industry *Rare Diseases: Considerations for the Development of Drugs and Biological Products* (December 2023) for more information on dose optimization in rare disease drug development, available at https://www.fda.gov/media/119757/download.

Page 5

- See the FDA Accelerating Rare Disease Cures (ARC) webpage available at https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/accelerating-rare-disease-cures-arc-program.
- See the FDA webpage with a list of guidance documents for Rare Disease Drug Development available at https://www.fda.gov/drugs/guidances-drugs/guidance-documents-rare-disease-drug-development.
- See the FDA webpage with funding opportunities for rare diseases at FDA available at https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/funding-opportunities-rare-diseases-fda.
- See the FDA Rare Disease Endpoint Advancement (RDEA) Pilot Program webpage available at https://www.fda.gov/drugs/development-resources/rare-disease-endpoint-advancement-pilot-program.
- See the FDA Complex Innovative Trial Design (CID) Meeting Program webpage available at https://www.fda.gov/drugs/development-resources/complex-innovative-trial-design-meeting-program.
- See the FDA Model-Informed Drug Development (MIDD) Paired Meeting Program webpage available at https://www.fda.gov/drugs/development-resources/model-informed-drug-development-paired-meeting-program.

- See the FDA Advancing Real-World Evidence (RWE) Program webpage available at https://www.fda.gov/drugs/development-resources/advancing-real-world-evidence-program.
- See the FDA Drug Development Tool Qualification Programs webpage available at https://www.fda.gov/drugs/development-approval-process-drugs/drug-development-tool-ddt-qualification-programs.
- See the Upcoming and Recent Events drop down menu on the FDA ARC program webpage for links to recordings of past meetings and workshops relevant to rare disease drug development available at https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/accelerating-rare-disease-cures-arc-program.
- See the FDA Biomarker Qualification Program webpage available at https://www.fda.gov/drugs/drug-development-tool-ddt-qualification-programs/biomarker-qualification-program.
- See the FDA Clinical Outcome Assessment (COA) Qualification Program webpage available at https://www.fda.gov/drugs/drug-development-tool-ddt-qualification-programs/clinical-outcome-assessment-coa-qualification-program.

Page 6

- See the Guidance Snapshot Pilot Program webpage available at https://www.fda.gov/drugs/guidances-drugs/guidance-snapshot-pilot.
- See the draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019) available at https://www.fda.gov/media/133660/download. When final, this guidance will reflect the Agency's current thinking on this topic.
- See the draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence* (September 2023) available at https://www.fda.gov/media/172166/download. When final, this guidance will reflect the Agency's current thinking on this topic.
- See guidance for industry *Rare Diseases: Considerations for the Development of Drugs and Biological Products* (December 2023) available at https://www.fda.gov/media/119757/download.
- See draft guidance for industry *Rare Diseases: Natural History Studies for Drug Development* (March 2019) available at https://www.fda.gov/media/122425/download. When final, this guidance will reflect the Agency's current thinking on this topic.
- See draft guidance for industry *Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products* (February 2023) available at https://www.fda.gov/media/164960/download. When final, this guidance will reflect the Agency's current thinking on this topic.
- See guidance for industry *Critical Path Innovation Meetings* (April 2015) available at https://www.fda.gov/media/89497/download.
- See draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (September 2023) available at https://www.fda.gov/media/172311/download. When final, this guidance will reflect the Agency's current thinking on this topic.
- See draft guidance for industry *Rare Diseases: Early Drug Development and the Role of Pre-IND Meetings* (October 2018) available at https://www.fda.gov/media/117322/download. When final, this guidance will reflect the Agency's current thinking on this topic.
- See guidance for industry Considerations for the Use of Real-World Data and Real-World Evidence To Support Regulatory Decision-Making for Drug and Biological Products (August 2023) available at https://www.fda.gov/media/171667/download.

- See guidance for industry *Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products* (December 2023) available at https://www.fda.gov/media/154449/download.
- See the FDA guidance search webpage for the most recent versions of guidance documents available at https://www.fda.gov/regulatory-information/search-fda-guidancedocuments.
- See guidance for industry *Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products* (July 2024) available at https://www.fda.gov/media/152503/download.
- See the FDA Patient-Focused Drug Development Guidance Series for Enhancing the Incorporation of the Patient's Voice in Medical Product Development and Regulatory Decision Making webpage available at https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical.
- See guidance for industry, Food and Drug Administration Staff, and other stakeholders *Patient-Focused Drug Development: Collecting Comprehensive and Representative Input* (June 2018) available at https://www.fda.gov/media/139088/download.
- See guidance for industry, Food and Drug Administration staff, and other stakeholders *Patient-Focused Drug Development: Methods to Identify What Is Important to Patients* (February 2022) available at https://www.fda.gov/media/131230/download.

Page 7

- Draft guidance for industry, Food and Drug Administration staff, and other stakeholders *Selecting, Developing or Modifying Fit-for-Purpose Clinical Outcomes Assessments* (June 2022) available at https://www.fda.gov/media/159500/download. When final, this guidance will reflect the Agency's current thinking on this topic.
- Draft guidance for industry, Food and Drug Administration staff, and other stakeholders *Incorporating Clinical Outcome Assessments into Endpoints for Regulatory Decision-Making* (April 2023) available at https://www.fda.gov/media/166830/download. When final, this guidance will reflect the Agency's current thinking on this topic.
- See the Biomarkers, Endpoints, and other Tools (BEST) Resource available at https://www.ncbi.nlm.nih.gov/books/NBK326791/.
- See FDA Glossary of Terms available at https://www.fda.gov/patients/clinical-trials-what-patients-need-know/glossary-terms.
- See CDER Small Business & Industry Assistance (SBIA): A Comprehensive Resource for Information on Human Drug Development in Regulation available at https://www.fda.gov/drugs/development-approval-process-drugs/cder-small-business-industry-assistance-sbia.