
Rare Diseases: Common Issues in Drug Development Guidance for Industry

DRAFT GUIDANCE

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

**February 2019
Rare Diseases
Revision 1**

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Rare Diseases: Common Issues in Drug Development Guidance for Industry¹

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

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I. INTRODUCTION

17 The purpose of this guidance is to assist sponsors of drug and biological products for the
18 treatment or prevention of rare diseases in conducting more efficient and successful drug
19 development programs.² Although the statutory requirements for marketing approval for drugs
20 to treat rare and common diseases are the same and issues discussed in this guidance are
21 encountered in other drug development programs, these issues are frequently more difficult to
22 address in the context of a rare disease for which there is often limited medical and scientific
23 knowledge, natural history data, and drug development experience.

24
25 This guidance revises and replaces the draft guidance for industry *Rare Diseases: Common*
26 *Issues in Drug Development* issued in August 2015. This revision includes the following:

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- Updates to the Natural History Studies section
 - Inclusion of issues for evaluation and validation of surrogate biomarkers
 - Description of nonclinical flexibility
 - Additional information on external controls and early randomization
 - Addition of a safety section
 - Retitled Chemistry, Manufacturing, and Controls section to Pharmaceutical Quality Considerations

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

² The term *drug* as used in this guidance refers to both human drugs and biological products unless otherwise specified.

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41 • Additional information on changes to drug substance or manufacturing process with
42 clarification on areas of flexibility

43

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

47

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

50

51 • Adequate description and understanding of the disease’s natural history

52

53 • Adequate understanding of the pathophysiology of the disease and the drug’s mechanism
54 of action

55

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

58

59 • Selection or development of outcome assessments and endpoints

60

61 • Evidence to establish safety and effectiveness

62

63 • Drug manufacturing considerations during drug development (e.g., pharmaceutical
64 quality system considerations)⁴

65

66 • Participation of patients, caretakers, and advocates in development programs

67

68 • Interactions with the Agency

69

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

74

75 This guidance does not contain discussion of the general issues of statistical analysis or clinical
76 trial design. Those topics are addressed in the ICH guidances for industry *E9 Statistical*

³ For recommendations on human gene therapy for rare diseases, see the draft guidance for industry *Human Gene Therapy for Rare Diseases* (July 2018). When final, this guidance will represent the FDA’s current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

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

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77 *Principles for Clinical Trials* (September 1998) and *E10 Choice of Control Group and Related*
78 *Issues in Clinical Trials* (May 2001), respectively.

79
80 In general, FDA’s guidance documents do not establish legally enforceable responsibilities.
81 Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only
82 as recommendations, unless specific regulatory or statutory requirements are cited. The use of
83 the word *should* in Agency guidances means that something is suggested or recommended, but
84 not required.

85

86

87 II. BACKGROUND

88

89 The Orphan Drug Act (the ODA) generally defines a rare disease or condition as one affecting
90 fewer than 200,000 people in the United States.⁵ Most rare diseases, however, affect far fewer
91 people. The ODA created a process for the Agency to designate a drug as a drug for a rare
92 disease or condition. The sponsor of a drug holding orphan drug designation may be eligible for
93 certain financial incentives intended to help make developing drugs for small numbers of patients
94 financially viable;⁶ however, the ODA does not create a statutory standard for the approval of
95 orphan drugs that is different from the standard for approval of drugs for common conditions.
96 Approval of any drug — for either a rare or a common disease or condition — must be based on
97 substantial evidence of the drug’s effectiveness for its intended use and sufficient information to
98 conclude that the drug is safe for use under the conditions prescribed, recommended, or
99 suggested in the proposed labeling. Sponsors should obtain evidence of effectiveness in an
100 identified population from adequate and well-controlled studies (see section VII., Evidence of
101 Safety and Effectiveness).⁷ FDA regulations provide flexibility in applying regulatory standards
102 because of the many types and intended uses of drugs. FDA “exercise[s] its scientific judgment”
103 in determining the kind and quantity of data a sponsor is required to provide for individual drug
104 development programs.⁸ This flexibility extends from the early stages of development to the
105 design of adequate and well-controlled studies required to demonstrate effectiveness to support
106 marketing approval and to establish safety data needed for the intended use.

107

108

⁵ See Public Law 97-414, 96 Stat. 2049 et seq. (1983) as amended by Public Law 98-551, 98 Stat. 2815, 2817 (1984), which added a numeric prevalence threshold to the definition of rare diseases. The ODA also defines a rare disease as any disease or condition that “affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug.” Section 526(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bb(a)(2)(B)).

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

⁷ See 21 CFR 314.126.

⁸ 21 CFR 314.105(c).

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109 **III. NATURAL HISTORY STUDIES**

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A. Considerations for Natural History Studies

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113 All drug development programs benefit from a firm scientific foundation, including an
114 understanding of disease natural history. The natural history of rare diseases is often poorly
115 understood, and the need for prospectively designed, protocol-driven natural history studies
116 initiated in the earliest drug development planning stages cannot be overemphasized. Although
117 FDA does not require natural history studies, we advise sponsors to evaluate early the depth and
118 quality of existing natural history knowledge to determine if it is sufficient to inform their drug
119 development programs. A natural history study initiated early may run in parallel with early
120 stages of drug development — including preclinical drug development — and may allow
121 updating of drug development strategies as new learning emerges.

122

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

124

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

129

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

132

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

134

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

139

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

142

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

147

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

150

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

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

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- Select data elements based on features of the disease, including signs and symptoms that are most important to patients (i.e., disease aspects most likely to be life limiting or life altering), potential prognostic characteristics, and disease features that may help formulate a sensitive clinical endpoint.¹¹ A sponsor should determine when specific disease manifestations are likely to develop and are likely to persist.
 - Collect data from clinical examination findings, laboratory measurements, imaging, reports of patient functioning and feeling,¹² and other relevant sources. The frequency of data collection is informed in part by knowledge of disease characteristics, such as the rate of deterioration of a patient condition and the presence or absence of exacerbations of a disease. Data should include the standards of care and concomitant therapies. A sponsor can modify the type and extent of data collection in a natural history study based on accumulated knowledge as the study proceeds.
 - Include patients across a wide spectrum of disease severity and phenotypes, rather than focus on a particular subtype. Broad inclusion criteria can allow identification and better characterization of disease phenotypes for which therapy development may be more feasible or needed.
 - Use standardized collection methods and medical terminology to enhance the value and usefulness of natural history study data.

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

175
176 See section VII., Evidence of Safety and Effectiveness, for discussion of natural history studies
177 as a source of data for historically controlled clinical trials.

B. Types of Natural History Studies

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

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1. Retrospective and prospective studies differ with respect to when patient data are collected. The information to be collected in the study is typically set forth in a protocol or procedure manual.
 - Retrospective natural history studies most commonly use information in existing medical records (e.g., patient charts). The included patients have defined characteristics such as diagnoses and outcomes.

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

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

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- Prospective natural history studies collect and analyze new data generated from identified patients at specified time points after the natural history study has been initiated.
 - 2. Cross-sectional and longitudinal natural history studies collect data from cohorts of patients. Cross-sectional and longitudinal studies may be retrospective or prospective.
 - Cross-sectional natural history studies collect data from individual patients at a single point in time. The point in time may be a specific date or set by stage of illness, date of diagnosis, onset of certain sign and symptoms, or other criteria.
 - Longitudinal natural history studies collect data from patients with the identified condition over time. The length of time and frequency of data collections can vary considerably and should be tailored to the characteristics of the disease.

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

217
218 For a prospective design, a cross-sectional study may be conducted more quickly than a
219 longitudinal study. However, cross-sectional studies are unable to provide a comprehensive
220 description of the course of progressive or recurrent disease. Cross-sectional studies may be
221 helpful to inform the design of a longitudinal natural history study. Longitudinal studies
222 typically yield the most comprehensive information about a disease, can characterize the course
223 of disease within patients, and can help distinguish different phenotypes.

224
225
226 **IV. DISEASE PATHOPHYSIOLOGY, CLINICAL MANIFESTATIONS, AND**
227 **IDENTIFICATION AND USE OF BIOMARKERS**

228
229 Knowledge about a disease's pathophysiology and clinical manifestations over time, which is
230 frequently incomplete for rare diseases, can be invaluable to the successful development of a
231 treatment, for example, by:

- 232
233
 - Identifying clinical manifestations of the disease that may have greater or earlier
234 responsiveness to treatment

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- 236 – Manifestations that are more closely linked to the disease pathophysiology and that
237 are targeted by the drug’s mechanism of action may be more likely to lead to clinical
238 benefits, especially if those manifestations are earlier in the disease course, when
239 intervention may be more beneficial.
- 240
- 241 • Estimating the amount of effect that may provide clinically meaningful benefit
 - 242
 - 243 • Identifying new biomarkers, or modifying the use of existing biomarkers that may
244 indicate effects on different steps in the pathophysiologic processes
 - 245
 - 246 – Predictive biomarkers may have critical roles in POC and dose-selection trials or in
247 identification of characteristics of patients with greater potential to respond to
248 therapy. Biomarkers that promptly indicate drug response might be used in a patient-
249 specific manner to individualize the treatment in dosage or regimen.
 - 250
 - 251 • Identifying early biomarkers of disease or effects of interventions and biomarkers that
252 could be used in adaptive and enrichment designs for greater efficiency.¹³
 - 253
 - 254 – For example, response of a laboratory measurement sensitive to drug effect could be
255 used to screen potential responders for inclusion in efficacy trials. Sponsors may also
256 be able to identify clinical or genomic characteristics that predict response using these
257 biomarkers.
 - 258

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

261

262 A surrogate endpoint is a marker, such as a laboratory measurement, radiographic image,
263 physical sign, or other measure, that is thought to be able to predict clinical benefit but is not
264 itself a measure of clinical benefit.¹⁴ Effects on some surrogate endpoints (e.g., blood pressure,
265 low-density lipoprotein cholesterol) are well established predictors of clinical benefit for certain
266 indications and are regularly used as the basis for traditional approval of drugs. Less well
267 established surrogate endpoints, but which are considered reasonably likely to predict clinical
268 benefit, may be used as a basis for accelerated approval for treatment of serious or life-
269 threatening diseases.

270

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

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

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

274
275 . . . a product for a serious or life-threatening disease or condition . . . upon a determination
276 that the product has an effect on a surrogate endpoint that is reasonably likely to predict
277 clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible
278 morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity
279 or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of
280 the condition and the availability or lack of alternative treatments.¹⁵

281
282 The use of a surrogate endpoint requires demonstration of analytical and clinical validation of the
283 biomarker test.

284
285 The analytic validity should be confirmed *before* starting the clinical trial. Analytical validation
286 evaluates several factors including the following:

- 287
- 288 • Sensitivity of the assay
 - 289
 - 290 • Specificity of the assay to measure the biomarker
 - 291
 - 292 • Range of results that can be measured
 - 293
 - 294 • Standardized methods of sample collection, shipment, and preparation
 - 295
 - 296 • Reproducibility of the results
 - 297

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

305
306

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

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

¹⁷ See the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (December 2017). When final, this guidance will represent the FDA's current thinking on this topic.

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

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307 V. NONCLINICAL STUDIES

308
309 Nonclinical studies are a mandated part of drug development.¹⁹ The goal of the nonclinical
310 program, which consists of in vitro and/or in vivo studies, is to provide evidence that the drug is
311 “reasonably safe to conduct the proposed clinical investigations.”²⁰ Nonclinical studies can also
312 contribute to a better understanding of the drug’s possible efficacy, mechanism of action,
313 pharmacokinetics, and metabolism. The data generated from nonclinical studies are important to
314 the design of early phase clinical trials, particularly for selecting the starting clinical dose, dose-
315 escalation plan, dosing regimen, and route of administration. The nonclinical data may help
316 guide the selection of patient eligibility criteria and will often determine important safety
317 monitoring procedures based on the observed toxicologic profile.

318
319 Internationally accepted guidances discuss the general design of nonclinical safety studies and
320 the timing of such studies relative to the conduct of a clinical development program.²¹
321 Regulations state that it is appropriate for FDA to exercise the broadest flexibility in applying the
322 statutory standards, while preserving appropriate guarantees for safety and effectiveness, for
323 drugs to treat serious and life-threatening diseases.²² This flexibility includes determining the
324 nonclinical data necessary to support clinical development programs. Factors that FDA
325 evaluates when determining areas of nonclinical flexibility include the pharmacological and
326 chemical characteristics of the drug, the design and objectives of the proposed clinical
327 investigations, the anticipated risks to humans, and the existing accumulated nonclinical
328 toxicology and human data. When determining the relevance of existing data, a sponsor may
329 consider factors such as drug product constituents, dosage form, route of administration, dose
330 levels, and dosing regimen plan.

331
332 For serious or life-threatening diseases where current treatments, if any, are inadequate, clinical
333 trials can often proceed with a modified nonclinical development program described in
334 guidances on nonclinical studies.²³ However, these trials may proceed only under limited
335 circumstances, with sufficient justification, and when no specific safety concern is present. For
336 example, FDA could consider toxicology studies in a single species or toxicology studies of less
337 than chronic duration to be sufficient to support clinical development. The ICH guidances for
338 industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and*
339 *Marketing Authorization for Pharmaceuticals* (January 2010) and *S6(R1) Preclinical Safety*

¹⁹ See 21 CFR 312.23(a)(8).

²⁰ *Ibid.*

²¹ See the ICH guidances for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* (January 2010); *S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* (July 1997); and *S9 Nonclinical Evaluation for Anticancer Pharmaceuticals* (March 2010). See also the draft guidance for industry *Investigational Enzyme Replacement Therapy Products: Nonclinical Assessment* (May 2015). When final, this guidance will represent the FDA’s current thinking on this topic.

²² See 21 CFR 312.80.

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

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340 *Evaluation of Biotechnology-Derived Pharmaceuticals* (July 1997) outline chronic toxicology
341 studies to support clinical indications of chronic, lifetime use. A chronic toxicity study calls for
342 a 6-month duration of dosing in a rodent and a 9-month duration of dosing in a nonrodent
343 species. If chronic toxicology studies are required, the sponsor may be able to conduct them
344 concurrently with clinical trials or in a staggered fashion, such that the resulting data from these
345 studies are submitted before dosing of any patient in an ongoing clinical trial that exceeds the
346 duration of the available nonclinical data. Sponsors should justify the use of such an approach.
347 In some cases, the sponsor may be able to delay submission of certain nonclinical studies to a
348 marketing application (e.g., reproduction and developmental toxicology studies) or defer
349 submission to the postmarketing period (e.g., carcinogenicity studies). FDA strongly encourages
350 a sponsor to discuss the proposed approach with the review division to obtain concurrence on
351 any abbreviated or deferred nonclinical program that could support the proposed clinical trials.²⁴
352

353 The sponsor should base the design of the pivotal toxicology studies on the biology of the
354 disease, expected pharmacology of the drug, existing POC data, proposed population to be
355 studied (e.g., adult versus pediatric), and proposed clinical trial design(s) for the clinical
356 indication being sought. Generally, healthy animals are the test system used in traditional
357 toxicology testing and, in most circumstances, should be the test system used to support clinical
358 trials. When an animal model of the disease is available, pharmacology and safety studies may
359 contribute to understanding the actions of the drug on disease pathophysiology, inform safety in
360 the context of that disease, and guide plans for measuring biological effects in patients.
361 Combined POC and safety studies in animal models of human disease have been utilized in
362 limited situations such as enzyme replacement therapy. Toxicology testing in an animal model
363 of disease may contribute to the nonclinical support for clinical trials but usually will not
364 substitute for toxicology testing in healthy animals.²⁵ However, safety evaluation in an animal
365 model may be particularly valuable when drug toxicity is predicted to be more severe in the
366 presence of disease pathophysiology.
367

368 When clinical trials are to be conducted in pediatric patients, POC data is required to establish a
369 prospect of direct benefit to the pediatric population.²⁶ Robust animal model results may support
370 the possibility of clinical benefit and the potential for a favorable benefit-risk assessment. For
371 many rare diseases, however, an animal disease model may not exist or may not exhibit some of
372 the clinically important manifestations of the disease. Sponsors should thoroughly understand
373 the biological relevance and limitations of the animal model of disease if it is used in nonclinical
374 studies. Sponsors can submit data from relevant in vitro models as supportive information.
375

²⁴ For recommendations on the substance and scope of nonclinical information needed to support clinical trials for cell therapy and gene therapy products, see the guidance for industry *Preclinical Assessment of Investigational Cellular and Gene Therapy Products* (November 2013).

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

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

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

379

380

VI. EFFICACY ENDPOINTS

382

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

387

388 Endpoint selection for a clinical trial involves understanding the following:

389

390 • The range and course of clinical manifestations associated with the disease. Sponsors can
391 often obtain this knowledge, along with possible differences among patient subtypes,
392 from a natural history study of the disease (see section III., Natural History Studies).

393

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

396

397 • The aspects of the disease that are meaningful to the patient and that could be assessed to
398 evaluate the drug's effectiveness.

399

400 • The possibility of using the accelerated approval pathway.²⁷

401

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

415

416 Clinical trials within a drug development program generally build upon the knowledge gained in
417 early studies to guide the design and endpoint selection for later stages of development.

418 Exploratory evidence from earlier phase trials helps inform the choice of dose and timing of

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

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419 endpoints. However, adaptive seamless trial designs may allow early evidence to be used later in
420 a study, especially helpful when there are limited numbers of patients to study.²⁸ If an adaptive
421 design is under consideration, a thorough statistical analysis plan including the key features of
422 the trial design and preplanned analyses should be discussed with the review division before trial
423 initiation.

424
425 Treatment-assignment blinding is important to lessen the potential for bias in trial results, but
426 ensuring perfect blinding is difficult for many treatments. An example of potential unblinding is
427 when all patients receiving an experimental drug develop a certain side effect or requires a
428 procedure/surgery, yet no patient in the placebo arm has the same side effect or procedure. When
429 the primary endpoint is clinically meaningful but susceptible to individual interpretation, the trial
430 may benefit from having additional supportive secondary endpoints (e.g., laboratory
431 measurements). Additionally, use of performance outcome assessments (e.g., cognitive tests,
432 ambulation tests), administered by trained health care professionals (blinded to treatment) and
433 standardized across patients and sites, may complement reports from caregivers and patients
434 regarding the relevant aspects of day-to-day functioning.

435
436 Sponsors should also consider the characteristics of an endpoint for the full range of patients,
437 including pediatric patients, to be enrolled into a clinical trial. For rare diseases, practical
438 considerations may warrant inclusion of a broader range of disease stages (e.g., severity of
439 manifestations, development of manifestations secondary to long-standing primary disease
440 manifestations) or phenotypes than might be used for trials in common diseases. The validity,
441 sensitivity, reliability, or interpretability of an endpoint may be different for patients with mild,
442 early-stage or slowly progressive forms of a disease compared to patients with severe, late-stage,
443 or rapidly progressive forms of the same disease.

444
445 Sponsors should consider approaches to trial design and assessment procedures that may
446 improve the utility of assessment tools. For example, a detailed description of procedures and
447 training for performing the assessment may improve the reliability of the assessment. An
448 assessment training program for investigators may improve both intra-rater and inter-rater
449 consistency. It is possible for sponsors to assess the adequacy/success of blinding at the end of a
450 trial. Effective blinding of treatments can reduce concern about bias in the subjective aspects of
451 an assessment, as can conduct of endpoint evaluation by raters not involved in other aspects of
452 the trial (e.g., radiologists, exercise testers). Another consideration is that rare disease clinical
453 development programs are often multinational, and sponsors should consider the effect of
454 language, culture, and customs on the interpretability and relevance of outcome assessments.

455
456 Sponsors considering the development of novel clinical outcome assessments should identify and
457 characterize these assessments early in their drug development programs. FDA advises sponsors
458 to consider using or modifying existing assessment measures for the disease under study because
459 evaluating novel measures is time consuming, with potential unexpected outcomes, and
460 evaluations initiated late in the process could delay drug development. At meetings with FDA,
461 sponsors should discuss the availability and modification of existing clinical outcome
462 assessments.

463

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

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VII. EVIDENCE OF EFFECTIVENESS AND SAFETY

The overall goals of drug development programs are to demonstrate the effectiveness of a drug in treating or preventing a disease or condition, to assess the magnitude and frequency of that effect, and to assess the risks of the drug, thereby enabling a benefit-risk assessment and appropriate labeling. In rare disease drug development, given the limited number of patients, it is crucial to standardize the collection and handling of data to ensure quality and interpretability. Increased measurement variability reduces power. Standardized operating procedures and quality assurance and quality control are essential. This is especially important when the trial is being conducted at multiple sites.

A. Effectiveness

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

- A clear statement of the trial objectives, a statement and rationale regarding planned sample size, and a summary of the methods of analysis being used
- A design that permits a valid comparison with a control that may be concurrent (e.g., placebo, standard of care, active treatment, dose comparison) or, in limited and special circumstances, historical
- Methods of patient selection that are well defined and result in the selection of an appropriate population for trial
- Methods that minimize bias in assigning patients to trial groups and ensure comparability between or among trial groups (e.g., randomization)

²⁹ Section 505(d) of the FD&C Act (21 U.S.C. 355(d)). For a biological product to be licensed under section 351 of the Public Health Service Act, a sponsor must demonstrate, among other things, that its product is safe, pure, and potent. Potency has long been interpreted to include effectiveness (21 CFR 600.3(s)).

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

³¹ 21 CFR 314.126(a).

³² 21 CFR 314.126(b).

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- 501 • Methods that minimize bias in trial conduct, outcome measures, and analysis (e.g.,
502 blinding techniques)
503
504 • Methods of assessment of patients' responses that are well defined and reliable (e.g.,
505 appropriate endpoints for the trial objectives).
506
507 • Methods of analysis adequate to assess effects of treatment (e.g., an appropriate statistical
508 analysis plan).
509

B. Use of Historical Controls and Early Randomization

510
511
512 Ultimately, registration trials must be designed to demonstrate whether an observed beneficial
513 effect is caused by the investigational intervention. Concurrent control designs and
514 randomization minimize unknown variables that could affect the outcome independent of the
515 intervention.
516

1. Historical (external) controls

517
518
519 For serious rare diseases with unmet medical need, interest is frequently expressed in using an
520 external, *historical*, control in which all enrolled patients receive the investigational drug, and
521 there is no randomization to a concurrent comparator group (e.g., placebo/standard of care). The
522 inability to eliminate systematic differences between nonconcurrent treatment groups, however,
523 is a major problem with that design. This situation generally restricts use of historical control
524 designs to assessment of serious disease when (1) there is an unmet medical need;³³ (2) there is a
525 well-documented, highly predictable disease course that can be objectively measured and
526 verified, such as high and temporally predictable mortality; and (3) there is an expected drug
527 effect that is large, self-evident, and temporally closely associated with the intervention.
528 However, even diseases with a highly predictable clinical course and an objectively verifiable
529 outcome measure may have important prognostic covariates that are either unknown or
530 unrecorded in the historical data.
531

532 As discussed in section III., Natural History Studies, when concurrent controls are impractical or
533 unethical, clinical trials can rely on a historical control. A natural history study providing
534 systematically and comprehensively captured data using uniform medical language and
535 methodologies relevant to the interventional clinical trials helps ensure that the historical control
536 is comparable to the treatment group. Natural history studies should be part of earliest drug
537 development. However, initiation of prospective natural history studies should not delay
538 interventional testing otherwise ready to commence for a serious disease with unmet medical
539 need.
540

2. Early randomization when feasible

541
542
543 In most cases, randomized controlled clinical trials are the most efficient and accurate way to
544 determine whether a drug has a clinically meaningful effect on the disease being treated.
545 Randomization of the first and all subsequently enrolled patients, including those in the earliest

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

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546 phases of clinical development, helps ensure that each patient’s contribution is interpretable,
547 avoiding potentially misleading findings from open-label, single-arm, externally controlled trials.
548 Stratified randomization (e.g., by important prognostic factors such as age or disease severity)
549 may be useful to improve comparability of trial groups.

550
551 Sponsors should explore and address concerns about control arms with patient and caregivers
552 stakeholder groups and clinical investigators early in planning stages to avoid undermining trial
553 recruitment and retention. Sponsors can sometimes address patient and family concerns by using
554 modified trial designs, when appropriate, to demonstrate effectiveness and interpretation of
555 safety signals. These designs retain the advantages of placebo-controlled trials and include
556 features that minimize placebo exposure and enhance access to experimental therapies (e.g.,
557 dose-response, delayed start, randomized withdrawal, crossover, adaptive designs with interim
558 analysis).

559
560 In all cases, it is important for patient and family stakeholder group members to understand that
561 because an investigational drug’s effectiveness, like its safety, is unknown, the placebo or
562 standard of care group may receive a net clinical benefit that is equal to or greater than that the
563 group receiving the investigational drug.

C. Safety

564
565
566
567 The goal of safety evaluation during drug development is to characterize the drug’s safety profile
568 in a reasonable number of patients over a reasonable duration of time, consistent with the
569 intended use of the drug. For the FDA, the term *reasonable* in the context of rare diseases means
570 consideration of feasibility challenges posed by the limited number of patients with the disease.

571
572 FDA interprets reference in the FD&C Act to the *safety* of a drug for the uses recommended in
573 labeling as meaning that the benefits of a drug outweigh its risks for those uses. Ultimately,
574 what is a feasible and sufficient safety assessment is a matter of scientific and regulatory
575 judgment based on the particular challenges posed by each drug and disease, including patients’
576 tolerance for risk in the setting of unmet medical need.³⁴

577
578 Regulations do not specify the needed evidence of safety, except that the evidence must include
579 adequate tests by all methods reasonably applicable.³⁵ The ICH guidance for industry *E1A The*
580 *Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-Term*
581 *Treatment of Non-Life-Threatening Conditions* (March 1995) describes expected exposure for
582 chronically used drugs for non-life-threatening conditions, but these expectations do not apply to
583 the many rare diseases that are life threatening. Although ICH E1A does not mention rare
584 diseases, the guidance states that a smaller number of patients may be acceptable when the
585 intended treatment population is small.

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

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

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586
587 Evidence-based decisions about what is feasible in terms of rare disease drug trial enrollment
588 depend on accurately estimated disease prevalence.³⁶ Many rare diseases are genetic in origin
589 and characterized by more than one phenotypic subtype (e.g., infantile, juvenile, adult).
590 Prevalence estimates should include all phenotypic subtypes of a disorder anticipated to respond
591 to the investigational drug. Sponsors also should determine prevalence estimates for all
592 countries in which trial sites are being considered. Sponsors should provide the individual
593 sources of current published prevalence estimates, rather than calculated averages, because
594 published prevalence estimates can vary widely depending on study details (e.g., case definition),
595 country or region, and advances in diagnostics and treatment over time. To facilitate discussion
596 with the review division about a feasible trial safety population enrollment goal, submissions
597 should include complete citations and, if possible, a copy of each reference pertaining to the
598 prevalence estimate.

599
600 FDA encourages sponsors to discuss their overall plans for maximizing the quantity and quality
601 of safety data in early drug development meetings with FDA. Several approaches for
602 augmenting the safety assessment are discussed below. FDA encourages sponsors to propose
603 additional strategies tailored to the specific challenges of their drug development programs.
604

- 605 • Natural history: As discussed in section III, Natural History Studies, knowledge about a
606 disease's natural history can inform many important aspects of trials. From a safety
607 perspective, this includes planning for disease-specific challenges to patient accrual and
608 retention to maximize the size of the premarket safety dataset. Robust natural history
609 data can also help distinguish drug-related adverse effects from underlying disease
610 manifestations.
- 611
612 • Trial eligibility: For rare diseases, it is especially important that inclusion and exclusion
613 criteria do not unnecessarily constrain patient eligibility for not only patient accrual but
614 for an adequate representation of the safety in the intended treatment population.
615 However, when appropriate, sponsors should consider enrichment strategies to decrease
616 heterogeneity (non-drug-related variability) and to enhance the ability of the clinical trial
617 to demonstrate a potential treatment effect.³⁷ Many rare diseases severely affect children,
618 and for diseases that affect both children and adults, sponsors should explore early
619 inclusion of pediatric patients in clinical studies.³⁸
620

³⁶ The term *prevalence* is used here in the context of a safety database, not in the context of orphan drug designation. Information about prevalence in orphan drug designation can be found on the FDA's Designating an Orphan Product: Drugs and Biological Products web page available at <https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/default.htm>.

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

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

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- 621 • Dose selection: Attention to dose selection is important to avoid patient discontinuations
622 because of lack of efficacy (dose too low) or unnecessary toxicity (dose too high),
623 especially when only one registration trial is feasible.
624
- 625 • Comparator arm: From a safety evaluation perspective, sponsors should use a concurrent
626 comparator arm design (e.g., placebo, no treatment, standard of care, active drug,
627 multiple doses), whenever ethically and practicably feasible, to facilitate interpretation of
628 adverse event causality, especially with respect to the incidence and severity of adverse
629 events that could be a manifestation of the disease under study.
630
- 631 • Auxiliary safety cohorts: Depending on details of the clinical development program, the
632 following approaches may augment the premarket safety database *if* the sponsor
633 rigorously collects and analyzes the data:
634
- 635 – A trial protocol with a safety cohort running parallel to the efficacy trial: This cohort
636 would include patients with the disease who investigators think might benefit from
637 the investigational drug but who do not meet all the registration trial eligibility
638 criteria. Such patients can be enrolled in the trial, avoiding the need for a separate
639 trial and protocol. However, these patients are not randomized and are excluded from
640 the efficacy analysis.
641
 - 642 – Patients receiving drugs under expanded access:³⁹ Systematic collection of expanded
643 access safety data might identify important premarketing signals that might otherwise
644 not be observed until the drug is used in the more diverse practice setting. Expanded
645 access programs can also randomize participants to more than one dose or duration of
646 therapy. Plans for these cohort should be discussed early in the development process
647 with the review divisions.
648
 - 649 – Relevant data from other sources, such as trials using the drug for other indications or
650 studies of similar drugs.⁴⁰
651

652 Sponsors should maintain communication with FDA as safety data accrue because timely
653 discussion of potentially needed postmarketing studies or risk mitigation measures beyond
654 labeling and routine pharmacovigilance facilitates submission of a complete marketing
655 application. This can help avoid preventable delays in access to an approved drug for patients

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

⁴⁰ New drug applications must include a “description and analysis of any other data or information relevant to an evaluation of the safety and effectiveness of the drug product obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from clinical investigations, including controlled and uncontrolled studies of uses of the drug other than those proposed in the new drug application, commercial marketing experience, reports in the scientific literature, and unpublished scientific papers.” 21 CFR 314.50(d)(5)(iv). If an applicant relies on FDA’s finding of safety or effectiveness for another drug or uses information to which it does not have a right of reference to fulfill a requirement for approval or licensure, FDA will not be able to consider the marketing application as a *stand-alone* application.

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656 with unmet medical need.⁴¹ For additional information refer to section X., Interactions With
657 FDA.

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VIII. PHARMACEUTICAL QUALITY CONSIDERATIONS

661

662 Drug manufacturing should undergo development concurrently with clinical development.
663 Review divisions encourage sponsors to discuss pharmaceutical quality development plans in
664 early-phase (such as at pre-investigational new drug application (pre-IND) meetings) and
665 throughout drug development to decrease the potential for developmental or approval delays
666 related to drug manufacturing.⁴²

667

668 FDA recommends that the sponsor carefully assess any planned changes to the drug substance or
669 drug product manufacturing process or drug product formulation at any phase of development to
670 determine if the changes could directly or indirectly affect the safety or efficacy of the product.
671 These assessments might include both nonclinical studies and clinical trials, should be conducted
672 with each change, and could inform whether bridging studies will be needed. Sponsors should
673 design adequate testing procedures early and implement them in a timely manner to mitigate
674 delays. To allow time to evaluate the potential effect of manufacturing changes on drug safety and
675 effectiveness and to minimize possible delays in development, manufacturing changes should be
676 made as early as feasible.

677

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

685

686 The need for larger amounts of the drug during later phase trials may lead to the need to modify
687 manufacturing procedures and purification methods. FDA also recognizes that transfer of
688 manufacturing responsibilities may occur after initial nonclinical and/or clinical investigations
689 (e.g., from a single investigator to a company, from a small company to a large company), which
690 may be a more common scenario for drugs for rare diseases. Any of these changes (even
691 changes expected to be minor) might result in unanticipated changes to drug characteristics (e.g.,
692 drug impurities, physical-chemical characteristics of proteins, cell phenotype of cellular
693 products). If significant differences are identified in drug characteristics after a manufacturing
694 change compared to drug batches (or biological product lots) used in earlier nonclinical studies
695 or clinical trials, then additional nonclinical studies and clinical trials may be needed because

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

⁴² See the draft guidance for industry *Rare Diseases: Early Drug Development and the Role of Pre-IND Meetings* (October 2018). When final, this guidance will represent the FDA's current thinking on this topic.

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696 these differences can raise concerns that the knowledge gained from the earlier studies will not
697 apply to further use of the drug. Examples of some of the many ways a change in drug
698 characteristics may adversely affect drug development include the following:

- 699
- 700 • The amount or type of impurities in a drug product used in clinical trials should be
701 comparable to the drug batches used in toxicology studies. Changes might raise concerns
702 that the drug used in later clinical trials has unknown toxicological characteristics.
703 Additional toxicology studies may be needed to evaluate the newly produced drug,
704 delaying the clinical development program.
 - 705
 - 706 • Changes in critical quality attributes of the planned commercial drug after the clinical
707 trials might raise concerns that the safety and effectiveness findings of the clinical trials
708 do not apply to the newly manufactured drug. This could warrant additional studies
709 (nonclinical, clinical, or both) to address the concern before marketing approval.

710

711 Given the wide variety of drugs, some of which are complex, FDA advises sponsors to consult
712 relevant guidances for industry (see References for a list of selected guidances).

713

714

715 IX. ADDITIONAL CONSIDERATIONS

716

717 A. Participation of Patients, Caregivers, and Advocates

718

719 FDA encourages involvement of patients, their caregivers, and advocates in the rare disease drug
720 development process. Their input may provide important information about their experiences,
721 perspectives, needs, and priorities related to potential endpoints and meaningful changes during
722 the review of an investigational drug. Patients can engage and provide input in numerous ways,
723 such as participating in advisory committees, serving as a disease-specific patient representative,
724 contributing to patient-focused drug development initiatives, providing solicited consultation on
725 scientific issues (e.g., clinically meaningful outcome measures), and participating in natural
726 history studies.⁴³ For drugs in development under an IND, FDA is subject to strict
727 confidentiality requirements and may not be able to discuss with the public specific information
728 about a drug development program.⁴⁴ In these situations, FDA encourages direct sponsor-patient
729 communication, when feasible, to facilitate the incorporation of patient perspectives and
730 experiences into the drug development process.

731

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

⁴⁴ For example, see 21 CFR 314.430.

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732 **B. Expedited Programs**

733
734 Most rare diseases are serious or life-threatening disorders with unmet medical needs and,
735 therefore, drugs treating these diseases may qualify for one or more expedited programs. FDA
736 encourages sponsors to consider these programs, which include fast track designation,
737 breakthrough therapy designation, priority review designation, and accelerated approval. For
738 details on eligibility and applications for expedited program designation, sponsors should consult
739 the guidance for industry *Expedited Programs for Serious Conditions — Drugs and Biologics*
740 (May 2014) and the draft guidance for industry *Expedited Programs for Regenerative Medicine*
741 *Therapies for Serious Conditions* (November 2017).⁴⁵
742

743 **C. Pediatric Considerations**

744
745 According to estimates, about half of the people affected by rare diseases are children.
746 Therefore, conducting studies to evaluate drugs in pediatric patients is critical for determining
747 the safety and efficacy of medications for many rare diseases.⁴⁶ When preparing development
748 plans, sponsors should consider whether the rare disease affects both children and adults or only
749 children. In general, sponsors should include pediatric patients with rare diseases in
750 premarketing clinical studies to develop data on the full range of people with the disease.
751

752 FDA strongly encourages sponsors to study the drug in all relevant pediatric populations, birth to
753 younger than 17 years of age, so that the drug can be properly and completely labeled for
754 pediatric use. As part of these pediatric studies, FDA encourages sponsors to develop pediatric
755 formulations of the drug to enable accurate dosing, down to the youngest children affected by the
756 rare disease.
757

758 For studies in which both pediatric and adult patients are included, the sponsor should consider
759 the relevance and comparability of endpoints to both groups including whether results from both
760 groups can be combined in a single statistical analysis. Importantly, there are additional
761 safeguards for pediatric patients enrolled in clinical studies beyond those provided for adult
762 patients.⁴⁷ These additional safeguards could limit the use of some procedures in children, which
763 would otherwise be acceptable for adults. Careful planning for a drug being developed to treat a
764 rare disease in children is important to maximize the efficiency and increase the likelihood of
765 success of the drug's clinical development program. Such planning should include discussions
766 with FDA early in drug development about the epidemiology of the rare disease and plans for
767 inclusion of pediatric patients in clinical studies.
768
769

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

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

⁴⁷ See 21 CFR part 50, subpart D.

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770 **X. INTERACTIONS WITH FDA**

771
772 FDA offers sponsors numerous opportunities for interaction. When developing an
773 investigational drug for a rare disease, FDA encourages sponsors to meet with the relevant drug
774 review division supporting development of that particular drug.⁴⁸ FDA's feedback to sponsors
775 may result in more efficient drug development. At the sponsor's request, FDA will, if possible,
776 provide advice on specific matters relating to an IND, including advice on the adequacy of data
777 to support an investigational plan, the design of a clinical trial, and whether proposed
778 investigations are likely to produce the data and information needed to meet requirements for a
779 marketing application.⁴⁹ FDA provides formal advice through milestone meetings (e.g., pre-IND
780 meeting, end of phase 1 meeting).

781
782 FDA can also provide informal support through interactions with FDA staff and offices (e.g.,
783 CDER including Rare Diseases Program and Professional Affairs and Stakeholder Engagement,
784 Center for Biologics Evaluation and Research (CBER), Office of Orphan Products Development,
785 Office of the Commissioner (Patient Affairs Staff).

786
787 For sponsors seeking early scientific and medical discussion for drug development
788 considerations, FDA has a forum called Critical Path Innovation Meetings (CPIM) in which
789 CDER staff and investigators from industry, academia, patient advocacy groups, and government
790 discuss improving efficiency and success in drug development.⁵⁰ In CPIM, CDER staff
791 members often provide general advice on how a technology or methodology might be used to
792 enhance drug development. CBER participates in CPIM meetings when cross-cutting issues
793 arise that involve both centers. In addition, CBER created the Initial Targeted Engagement for
794 Regulatory Advice on CBER Products (INTERACT) meeting program for potential sponsors to
795 engage with CBER staff and obtain advice on a specific topic or issue that is critical to early drug
796 product development. The advice provided by CBER staff to a potential sponsor during an
797 INTERACT meeting may help streamline development by, for example, helping sponsors to
798 avoid unnecessary preclinical studies.

799

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

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

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

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Draft guidances for industry²

Adaptive Design Clinical Trials for Drugs and Biologics

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

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

Expedited Programs for Regenerative Medicine Therapies for Serious Conditions

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

Human Gene Therapy for Rare Diseases

Investigational Enzyme Replacement Therapy Products: Nonclinical Assessment

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

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

Draft guidance for industry, FDA staff, and other stakeholders³

Patient-Focused Drug Development: Collecting Comprehensive and Representative Input

Guidances for FDA reviewers and sponsors

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

Guidances for industry

CGMP for Phase 1 Investigational Drugs

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

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

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

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

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838	<i>Critical Path Innovation Meetings</i>
839	
840	<i>Determining the Extent of Safety Data Collection Needed in Late-Stage Premarket and</i>
841	<i>Postapproval Clinical Investigations</i>
842	
843	<i>Expanded Access to Investigational Drugs for Treatment Use — Questions and Answers</i>
844	
845	<i>Expedited Programs for Serious Conditions—Drugs and Biologics</i>
846	
847	<i>Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products</i>
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849	<i>Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment</i>
850	
851	<i>Patient-Reported Outcome Measures: Use in Medical Product Development to Support</i>
852	<i>Labeling Claims</i>
853	
854	<i>Potency Tests for Cellular and Gene Therapy Products</i>
855	
856	<i>Preclinical Assessment of Investigational Cellular and Gene Therapy Products</i>
857	
858	<i>Premarketing Risk Assessment</i>
859	
860	<i>Process Validation: General Principles and Practices</i>
861	
862	<i>Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products</i>
863	
864	Guidance for industry and FDA staff
865	<i>Qualification Process for Drug Development Tools</i>
866	
867	Guidance for industry and review staff
868	<i>Best Practices for Communication Between IND Sponsors and FDA During Drug Development</i>
869	
870	ICH guidances for industry
871	<i>E1A, The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for</i>
872	<i>Long-Term Treatment of Non-Life-Threatening Conditions</i>
873	
874	<i>E4 Dose-Response Information to Support Drug Registration</i>
875	
876	<i>E6 Good Clinical Practice: Consolidated Guidance</i>
877	
878	<i>E8 General Considerations for Clinical Trials</i>
879	
880	<i>E9 Statistical Principles for Clinical Trials</i>
881	
882	<i>E10 Choice of Control Group and Related Issues in Clinical Trials</i>
883	

Contains Nonbinding Recommendations

Draft — Not for Implementation

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

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

889
890 *Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their*
891 *Manufacturing Process*

892
893 *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and*
894 *New Drug Products: Chemical Substances*

895
896 *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological*
897 *Products*

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899 *Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients*

900
901 *Q10 Pharmaceutical Quality System*

902
903 *S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals*

904
905 *S7A Safety Pharmacology Studies for Human Pharmaceuticals*

906
907 *S9 Nonclinical Evaluation for Anticancer Pharmaceuticals*

908
909 **Other resources**

910 FDA, Food and Drug Administration Safety and Innovation Act (FDASIA) Section 1137:
911 Patient Participation in Medical Product Discussions Report on Stakeholder Views, January
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