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# 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## *DRAFT GUIDANCE*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)**

**August 2015  
Rare Diseases**

# Rare Diseases: Common Issues in Drug Development Guidance for Industry

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*Contains Nonbinding Recommendations*

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# Rare Diseases: Common Issues in Drug Development Guidance for Industry<sup>1</sup>

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

## I. INTRODUCTION

This guidance assists sponsors of drug and biological products<sup>2</sup> intended to treat or prevent rare diseases in conducting more efficient and successful development programs through a discussion of selected issues commonly encountered in rare disease drug development. Although similar issues are encountered in other drug development programs, they are frequently more difficult to address in the context of a rare disease with which there is often little medical experience. These issues are also more acute with increasing rarity of the disorder. A rare disease is defined by the Orphan Drug Act of 1983 as a disorder or condition that affects less than 200,000 persons in the United States.<sup>3</sup> Most rare diseases, however, affect far fewer persons.

This guidance addresses the following important aspects of drug development:

- Adequate description and understanding of the disease's natural history
- Adequate understanding of the pathophysiology of the disease and the drug's proposed mechanism of action
- Nonclinical pharmacotoxicology considerations to support the proposed clinical investigation or investigations

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<sup>1</sup> 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 (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

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

<sup>3</sup> Public Law 97-414, 96 Stat. 2049 (1983). Amended by Public Law 98-551 (1984) to add a numeric prevalence threshold to the definition of rare diseases.

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- Reliable endpoints and outcome assessment
- Standard of evidence to establish safety and effectiveness
- Drug manufacturing considerations during drug development

Early consideration of these issues allows sponsors to efficiently and adequately address them during the course of drug development, from early exploratory studies to confirmatory efficacy and safety studies, and to have productive meetings with FDA. These and other issues, as they apply to all drug development programs, are also considered in FDA and International Conference on Harmonisation (ICH) guidances (see References for selected guidances).

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

## **II. BACKGROUND**

The Orphan Drug Act provides incentives associated with orphan-drug designation<sup>4</sup> to make developing drugs for small numbers of patients financially viable; however, it does not create a statutory standard for the approval of orphan drugs that is different from the standard for drugs for common conditions. Approval of all drugs – for both rare and common conditions – must be based on demonstration of substantial evidence of effectiveness in treating or preventing the condition and evidence of safety for that use. Evidence of effectiveness should be obtained from one or more adequate and well-controlled studies in an identified population (see section VII, Evidence of Effectiveness and Safety).<sup>5</sup> FDA acknowledges that certain aspects of drug development that are feasible for common diseases may not be feasible for rare diseases. FDA regulations provide flexibility in applying regulatory standards because of the many types and intended uses of drugs. FDA “exercise[s] its scientific judgment” in determining the kind and quantity of data a sponsor is required to provide for individual drug development programs.<sup>6</sup> This flexibility extends from early phases of development to design of adequate and well-controlled clinical studies required to demonstrate safety and effectiveness to support marketing approval.

Many rare disorders are serious conditions with no approved treatments, leaving substantial unmet medical needs for patients. FDA recognizes that rare diseases are highly diverse and is

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<sup>4</sup> Ibid.

<sup>5</sup> 21 CFR 314.126

<sup>6</sup> 21 CFR 314.105

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77 committed to helping sponsors create successful drug development programs that address the  
78 particular challenges posed by each disease.

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### **III. NATURAL HISTORY STUDIES**

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83 All drug development programs should have a firm scientific foundation, and understanding the  
84 natural history of a disease is an important element in this foundation. Because of the small  
85 numbers of patients affected, and with clinical experience dispersed among a small number of  
86 clinical referral centers, the natural history of rare diseases is often poorly described. FDA  
87 advises sponsors to evaluate the depth and quality of existing natural history knowledge early in  
88 drug development. FDA does not require that natural history studies be conducted, but when  
89 knowledge about the disease is insufficient to guide clinical development, a well-designed  
90 natural history study may help in designing an efficient drug development program.

91

92 In-depth understanding of the disease helps sponsors avoid mistakes that may be costly in time  
93 and resources. Efficient study of the small number of affected patients may be guided better by  
94 greater understanding of the disease. A natural history study can provide critical information to  
95 guide every stage of drug development from drug discovery to determining effectiveness and  
96 safety of the drug in treating a disease. Knowledge about the disease's natural history can  
97 inform important aspects of drug development including:

98

- 99 • Defining the disease population, including a description of the full range of disease  
100 manifestations and identification of important disease subtypes
- 101
- 102 • Understanding and implementation of critical elements in clinical study design, such as  
103 study duration and choice of subpopulations
- 104
- 105 • Developing and selecting outcome measures that are more specific or sensitive to  
106 changes in the manifestations of the disease or more quickly demonstrate safety or  
107 efficacy than existing measures.
- 108
- 109 • Developing new or optimized biomarkers that may provide proof-of-concept (POC)  
110 information, guide dose selection, allow early recognition of safety concerns, or provide  
111 supportive evidence of efficacy. In some cases, biomarkers can be used for surrogate  
112 endpoints.<sup>7</sup>

113

114 No single set of data elements adequately describes all rare diseases. Rare diseases are highly  
115 diverse and as a group affect many organ systems with wide variations in the rates and patterns  
116 of manifestations and progression. Selection of the data elements to collect in a natural history  
117 study should be broad and based on features of the disease, including morbidities that are most  
118 important to patients (i.e., disease aspects most likely to be life-limiting or life-altering),  
119 potential prognostic characteristics, and disease features that, even if not serious aspects of the

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<sup>7</sup> See References, including the guidance for industry *Expedited Programs for Serious Conditions — Drugs and Biologics*.

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120 disease, may help formulate a sensitive clinical endpoint. It is critical to know, for example,  
121 which disease manifestations are likely to develop and when, and which are likely to persist. It  
122 is also critical to identify disease signs that predict the development of the most important  
123 disease manifestations. The types of data to collect may include clinical examination findings,  
124 laboratory measurements, imaging, and patient reports of function and feeling. The frequency of  
125 data collection is informed in part by knowledge of disease characteristics, such as the rate of  
126 deterioration and the presence or absence of exacerbations of a disease. The type and extent of  
127 data collection in a natural history study may be modified based on accumulating knowledge.

128  
129 Because there is substantial phenotypic variability in many rare disorders, FDA recommends that  
130 natural history studies include patients across as wide a spectrum of disease severity and  
131 phenotypes as possible, rather than focusing too early on a particular subset. This broad  
132 inclusion can allow identification and better characterization of disease phenotypes for which  
133 therapy development may be more feasible or needed. Understanding whether there is a  
134 continuous range of, or distinctly separable, phenotypes can greatly alter the drug development  
135 program.

136  
137 Natural history data should be collected for a sufficient duration to capture clinically meaningful  
138 outcomes and determine variability in the course of the disease. Although the emphasis in this  
139 section is on the use of natural history studies as critical background information, such studies  
140 may be continued during clinical development to assess the suitability of new measurement tools  
141 and outcome measures for use in future treatment trials.

142  
143 The data for natural history studies can be collected prospectively or retrospectively, but  
144 prospective longitudinal natural history studies are likely to generate the most useful information  
145 about a disease. Prospective studies can be designed to systematically and comprehensively  
146 capture data using consistent medical terms relevant to future clinical studies. Data collected  
147 retrospectively from clinical care chart review may be incomplete or difficult to interpret. For  
148 example, these data may not include concomitant medication information or evaluation of  
149 disease features of particular interest, or they may be encoded with varying medical terms for the  
150 same clinical condition. Longitudinal studies characterize the course of disease within  
151 individuals and better enable different phenotypes to be distinguished.

152  
153 The potential use of natural history data as a historical comparator for patients treated in a  
154 clinical trial is often of interest but the challenges associated with the use of historical controls  
155 are well recognized. Although comparability of study patients with historical controls on known  
156 covariates can be assessed, comparability on subjectively influenced measures or unknown  
157 covariates is more difficult to assure. Even diseases thought to have tightly stereotyped, rapidly  
158 progressive clinical courses and objectively verifiable outcomes (e.g., mortality) may have  
159 important prognostic covariates either unknown or unrecorded in the historical data. While  
160 studies with historical controls have been used in clinical development programs of rare diseases,  
161 historical controls may be unsuitable for adequate and well-controlled studies in many  
162 circumstances. In general, studies using historical controls are credible only when the observed  
163 effect is large in comparison to variability in disease course (e.g., substantial improvement in  
164 outcome is observed with treatment in a disease that does not naturally remit).

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### **IV. DISEASE PATHOPHYSIOLOGY AND IDENTIFICATION AND USE OF BIOMARKERS**

General knowledge about a rare disease’s pathophysiology is frequently incomplete. FDA does not require sponsors to study the biochemical basis of a disease, but sponsors should seek to understand the pathophysiology of a disease as fully as possible at the outset of drug development. Knowledge about a disease’s pathophysiology and how it is clinically manifest over time can be invaluable to successful development of a treatment in a number of ways:

- Identifying clinical manifestations of the disease that may have greater or earlier responsiveness to treatment. These disease manifestations may be useful in the design of study endpoints. For example, manifestations that are dynamically linked to the severity of the pathophysiology may more readily show a response to treatment. Manifestations of the disease that are the result of long-standing pathophysiologic processes may be less responsive than those that are the result of acute processes.
- Estimating the amount of effect on the drug target that may provide clinically meaningful effects. For example, if there are distinct phenotypes differentiated by pathophysiologic severity, it might be possible to target a drug effect to lessen the pathophysiological severity and alter a more severe phenotype, making it more like a less severe phenotype.
- Estimating when to test the treatment in patients in the course of the disease. If some disease manifestations occur later than when the patients could be identified and enrolled in a study, then targeting patients for treatment before secondary manifestations develop may be important.
- Estimating the schedule of drug administration that will provide adequate drug exposure. The rate of pathophysiologic response to drug action on the target, both onset of action and washout, may guide the selection of drug regimen. For example, if a limited duration of drug exposure produces a long-lasting alteration in a critical pathophysiologic process, then a treatment administration schedule that does not ensure continuous exposure may be sufficient. In contrast, if the pathophysiologic process is rapidly reestablished after loss of drug exposure, more frequent drug administration may be needed.
- Identifying therapeutic targets that may lead to drug candidates for nonclinical and clinical testing.
- Identifying new biomarkers, or refining existing ones, that may indicate effects on different steps in the pathophysiologic processes. These biomarkers may have critical roles in POC and dose selection studies, or in identifying characteristics of patients with a greater potential to respond to therapy. Biomarkers that promptly indicate drug response might be used in a patient-specific manner to individualize the treatment in dosage or regimen.



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- 211       • Identifying early markers and responses that could be used in adaptive and enrichment  
212 designs for greater efficiency.<sup>8</sup> For example, response of an early laboratory  
213 measurement sensitive to drug effect could be used as a screen to identify potential  
214 responders for inclusion in efficacy trials. It also may be possible to identify patient or  
215 genomic characteristics that predict response using these early markers.

216  
217 Substantial amounts of drug development work have not been done for most rare diseases and  
218 well-developed assays with the potential to serve as informative biomarkers may not be  
219 available. When such biomarkers are to be used in a drug development program, a reliable and  
220 sufficiently sensitive assay should be developed early in advance of initiating clinical studies that  
221 will rely on measurement of that biomarker. Similar concerns also may apply to other types of  
222 pathophysiologic markers such as imaging.

223  
224 Sponsors should consider applying pathophysiologic knowledge and developing disease  
225 biomarkers early in the drug development program. Although some decisions during drug  
226 development might be guided entirely by accumulated clinical trial results, drug development  
227 may be more efficient when informed by detailed knowledge about pathophysiologic processes.  
228 Starting research early to improve understanding of the pathophysiology may help to shorten a  
229 drug development program.

230  
231 FDA recommends that sponsors discuss the available knowledge about disease pathophysiology,  
232 the drug mechanism, and downstream effects of drug activity at initial meetings with FDA,  
233 including pre-investigational new drug application (pre-IND) meetings. Sponsors should  
234 discuss how to evaluate the drug-target interaction and downstream aspects of the disease  
235 process. These discussions can be instrumental in guiding the clinical program.

## 236 237 238 **V. NONCLINICAL STUDIES**

239  
240 As a general matter, nonclinical studies are a necessary part of drug development for both rare  
241 and common diseases.<sup>9</sup> Before first-in-human use of an investigational drug, FDA requires  
242 toxicology information from in vitro studies, animal studies, or both. These nonclinical studies  
243 provide essential evidence that the drug is “reasonably safe to conduct the proposed clinical  
244 investigation.”<sup>10</sup> Nonclinical studies can also contribute to a better understanding of the drug’s  
245 mechanism of action. The data generated from nonclinical studies are important to the design of  
246 the early stage clinical trials, particularly for selecting the starting clinical dose level, dose-  
247 escalation plan, dosing regimen, and route of administration. The nonclinical data may help  
248 guide patient eligibility criteria and will often determine some important safety monitoring  
249 procedures.

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<sup>8</sup> See References, including 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*. When final, these guidances will represent the FDA’s current thinking on these topics.

<sup>9</sup> 21 CFR 312.23(a)(8)

<sup>10</sup> *Ibid.*

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251 Sponsors should base toxicology study design on the biology of the disease, expected  
252 pharmacology of the drug, existing POC data, clinical trial design or designs to be proposed, and  
253 the indication being sought. Healthy animals generally are the test system used in traditional  
254 toxicology testing and, in most circumstances, should be the test system used to support clinical  
255 trials. Internationally accepted, general guidances are available for the timing and nature of  
256 nonclinical safety studies relative to clinical trials in drug development.<sup>11</sup> These guidances also  
257 describe potential areas of FDA flexibility in determining the nonclinical data necessary to  
258 support an evolving clinical development program. Among the factors FDA considers are the  
259 design and objectives of the proposed clinical investigations, the existing accumulated  
260 nonclinical and human data and experience with the drug, and the possible risks to humans.  
261 Information from previous nonclinical and human use has the potential to decrease the amount of  
262 new toxicology data needed. Factors such as drug constituents, dosage form, route, and dose and  
263 regimen of administration may be considered in determining the relevance of prior data. FDA  
264 also considers the diverse biology and structure of drugs and biologics (e.g., chemically  
265 synthesized drug products, recombinant protein products, plasma-derived products, cell therapy  
266 products, and gene therapy products)<sup>12</sup> in determining the nonclinical data necessary.  
267  
268 FDA may apply additional flexibility in evaluating development programs for drugs to treat  
269 serious and life-threatening disorders.<sup>13</sup> Under limited circumstances, clinical studies can  
270 proceed in the absence of standard toxicology studies; however, this approach should be well  
271 justified and is only appropriate for serious or life-threatening diseases where current treatments,  
272 if any, are inadequate. In these circumstances, we strongly recommend that sponsors meet with  
273 FDA before starting animal studies to obtain concurrence with an abbreviated nonclinical  
274 program that can support the proposed clinical trials.  
275  
276 When an animal model of the disease is available, pharmacology studies may contribute to  
277 understanding the actions of the drug on disease pathophysiology and guide plans for measuring  
278 biological effects in patients. Toxicology testing in an animal model might be performed, but  
279 usually will not substitute for all toxicology testing in healthy animals because of concern that  
280 the disease pathophysiology may obscure some drug toxicity. Safety evaluation in an animal  
281 model also may be particularly valuable when it is suspected that drug toxicity may be more  
282 severe in the presence of disease pathophysiology.  
283

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<sup>11</sup> See the ICH guidances for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* and *S6 (R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals*. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

<sup>12</sup> For recommendations on the substance and scope of nonclinical information needed to support clinical trials for cell therapy and gene therapy products, refer to the guidance for industry *Preclinical Assessment of Investigational Cellular and Gene Therapy Products* on the Cellular & Gene Therapy Guidances Web page at <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/default.htm>.

<sup>13</sup> 21 CFR 312.80, subpart E

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284 FDA generally does not require that the sponsor perform testing for safety or pharmacologic  
285 activity in an animal model of a disease. In some cases, however, such as for therapies that  
286 might have long-lasting or irreversible adverse effects, animal model studies showing a drug's  
287 potential for beneficial activity may be valuable in supporting a conclusion that risks of the drug  
288 are not unreasonable in light of the potential for benefit.<sup>14</sup> For many rare diseases, however, an  
289 animal disease model may not exist or may not exhibit some clinically important manifestations  
290 of the disease. Sponsors should thoroughly understand the biological relevance and limitations  
291 of the animal model of disease if used in nonclinical studies.

292  
293 In a nonclinical development program, *in vitro* and *in vivo* investigations for drug discovery and  
294 POC commonly precede toxicology studies. If care is taken to preserve the organs, tissues, and  
295 other samples during nonclinical studies focused on drug discovery and POC, toxicological  
296 analyses might be deferred on these samples until there is confidence that the specific molecule  
297 used in the animal study will be relevant to the human clinical trial. Although these analyses  
298 alone usually do not provide a sufficient toxicological evaluation before clinical studies, this  
299 information might supplement toxicology-focused studies.

300  
301 The timing and specific design of nonclinical studies vary with the type of drug or biological  
302 product being studied, the information needed to support administration in the initial human  
303 studies and later stages of drug development, and the intended clinical use. FDA encourages  
304 sponsors to seek early communication with FDA, such as at pre-IND meetings, to discuss an  
305 appropriate nonclinical development program for the investigational product. Such discussions  
306 can facilitate the timely conduct of clinical trials, and may reduce the use of animals and other  
307 drug development resources.

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### **VI. EFFICACY ENDPOINTS**

310  
311  
312 The selection of appropriate endpoints is critical for a clinical trial to meet its objectives. For  
313 many rare diseases, well-characterized efficacy endpoints appropriate for the disease are not  
314 available. Defining a study endpoint includes selecting a patient assessment to be used as an  
315 outcome measure and the times in the study when the patient will be assessed. Early in drug  
316 development, sponsors should begin to consider the available patient assessment tools and assess  
317 their suitability. Sponsors should recognize the need to develop new assessment tools, or modify  
318 existing ones, early to maximize time to develop and evaluate a new tool before relying upon it  
319 as the basis of an endpoint in a clinical trial.

320  
321 Endpoint selection for a clinical trial entails multiple considerations including:

- 322
- 323 • An understanding of the disease, including the likelihood, range, and course of clinical  
324 manifestations associated with the disease (disease definition). Sponsors can often obtain  
325 this knowledge, along with disease characteristics of patient subsets, from a natural  
326 history study of the disease (see section III, Natural History Studies).
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<sup>14</sup> 21 CFR 312.42(b)

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- 328 • An understanding of the clinical characteristics (manifestations and timing) of the  
329 specific population targeted by the drug (which may be a subset of the total population  
330 with a disease).  
331
- 332 • An understanding of which aspects of the disease are meaningful to the patient and might  
333 also be affected by the drug’s activity. This evaluation is influenced by knowledge of the  
334 pathophysiology of the disease and prior experience (if any) with the drug or related  
335 drugs, including nonclinical and clinical effects and pharmacology.  
336
- 337 • Knowledge of what patient assessments exist or might be refined or developed for use as  
338 outcome assessment tools to measure selected aspects of the disease.  
339

340 A detailed understanding of assessment tools’ characteristics guides selection among multiple  
341 tools that might be considered for outcome assessment. Characteristics of an assessment tool  
342 that are important to consider when evaluating its potential for use in a study endpoint include:  
343

- 344 • Validity, that is, how well scores used to define a study endpoint represent the selected  
345 aspects of the disease reflected in the objectives of the clinical trial.  
346
- 347 • Reliability, including inter-rater and intra-rater (test-retest) reliability. Reliability is  
348 especially important when clinical trials assess small numbers of patients.  
349
- 350 • Feasibility, including expense, tolerability, and availability of any specialized equipment  
351 or skills necessary to perform the assessment. For example, rare disease clinical trials are  
352 often conducted at a small number of centers that have the appropriate specialized  
353 equipment, and long travel distances for patients may be a barrier. In other cases,  
354 complex patient assessments capable of detecting small changes may rely upon  
355 procedures that are difficult and poorly accepted by the patient. Both may hinder patient  
356 enrollment or completeness of study visits.  
357
- 358 • Resistance to bias. Although treatment-assignment blinding is important to lessening the  
359 potential for bias in study results, ensuring perfect blinding is difficult for many  
360 treatments. An assessment that is less readily influenced by a patient’s or investigator’s  
361 knowledge of treatment assignment can improve confidence in the study results.  
362
- 363 • Ability to detect change. Assessments that are more finely detailed, with commensurate  
364 reliability, may offer the potential to detect smaller changes in a disease manifestation  
365 that it is intended to measure (i.e., the potential for greater sensitivity to clinical effects).  
366
- 367 • Relationship to meaningful symptoms or function. Some assessments directly measure  
368 the symptoms or functional abilities that are important to understand treatment benefit in  
369 the patient with the disease of interest. Other assessments, such as clinical outcome  
370 assessments and certain biomarkers used as surrogate endpoints do not directly measure  
371 these but are used to predict clinical benefit. This relationship should be taken into  
372 consideration.  
373

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- 374       • Clinical interpretability. The clinical meaning of changes in an outcome assessment  
375       should be understood within the context of the disease and population being studied. The  
376       clinical meaning and importance of the observed effects of the drug influence the final  
377       benefit-risk comparison made both by FDA in determining whether to grant marketing  
378       approval and by health care providers in determining whether to prescribe the marketed  
379       drug.

380  
381 Sponsors may also consider approaches to study design and procedures for applying the patient  
382 assessment as an endpoint in a clinical trial that may improve the utility of the assessment tool.  
383 For example, a detailed description of procedures for performing the assessment may improve  
384 the reliability of the assessment. This can be particularly important for small clinical trials. An  
385 assessment tool training program for investigators may improve both intra-rater and inter-rater  
386 (i.e., across study sites) consistency. As another example, effective blinding of treatments can  
387 reduce concern about bias in the subjective aspects of an assessment, as can conduct of endpoint  
388 evaluation by people not involved in other aspects of the trial (e.g., radiologists, exercise testers).

389  
390 Sponsors should be aware that the endpoint used to demonstrate efficacy often will not be the  
391 best endpoint for all studies in a development program. Sponsors should select endpoints  
392 considering the objectives of each study in the context of the overall clinical development  
393 program. Different endpoints are often advantageous for the evolving objectives of successive  
394 clinical trials. The earliest clinical investigations usually will focus on safety assessments and  
395 also can be useful in evaluating drug pharmacokinetics and pharmacodynamic effects. Early and  
396 middle period clinical investigations should be designed to guide selection of dose strength and  
397 frequency, and may rely on pharmacodynamic or intermediate clinical effects (i.e., prompt  
398 response). Later clinical investigations are generally designed to provide the clearest  
399 determinations of efficacy and safety. Clinical outcome assessments are usually the basis of  
400 endpoints of adequate and well-controlled studies (section VII) that will provide the substantial  
401 evidence of effectiveness supporting marketing approval of the drug. All of these considerations  
402 should be addressed during the course of drug development, although development programs in  
403 rare diseases often are compressed into as few trials as feasible.

404  
405 Clinical trials within a drug development program generally build upon the knowledge gained in  
406 early studies to guide the design and endpoint selection for later phases of development. A drug  
407 development program consisting of only a single trial intended to demonstrate the safety and  
408 effectiveness of a drug may fail due to insufficient exploratory evidence gained from earlier  
409 phases of study.

410  
411 Different endpoints have different combinations of characteristics. Ability to readily detect  
412 change may be more important than clinical meaningfulness for an early phase trial with a POC  
413 primary objective. In contrast, clinical meaningfulness is an important endpoint characteristic in  
414 a study intended to provide evidence of effectiveness to support a marketing application.  
415 Including several endpoints with different characteristics may improve the overall interpretability  
416 of the study results. For example, a phase 3 clinical trial with a clinically meaningful but  
417 subjective primary efficacy endpoint (i.e., one that may be prone to bias) may benefit from  
418 having secondary endpoints that are resistant to bias (such as laboratory measurements).

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420 Sponsors should also consider the characteristics of an endpoint for the full range of patients to  
421 be enrolled into a clinical trial. For rare diseases, practical considerations may warrant inclusion  
422 of a broader range of disease stage (e.g., severity of manifestations, development of  
423 manifestations secondary to long-standing primary disease manifestations) or phenotype than  
424 might be used for studies of common diseases. The validity, sensitivity, reliability, or  
425 interpretability of an endpoint may be different for patients with early-stage or slowly  
426 progressive forms of a disease as compared to patients with severe, late-stage, or rapidly  
427 progressive forms of the same disease.

428  
429 Identifying and characterizing potential clinical assessments can be time-consuming, and  
430 sponsors should start these processes at the outset of the clinical development program.  
431 Sponsors might not complete characterization or refinement of clinical assessments used as  
432 endpoints by the time of endpoint selection for confirmatory studies if initiated late in the clinical  
433 program, thus delaying drug development. FDA advises sponsors to consider the  
434 appropriateness of existing tools for the disease under study, and to discuss the availability of  
435 appropriate endpoints and strategies to develop or refine endpoints at all meetings with FDA.

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### **VII. EVIDENCE OF EFFECTIVENESS AND SAFETY**

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The overall goals of drug development programs are to evaluate whether a drug is effective in  
treating or preventing a disease or condition, assessing the magnitude and frequency of that  
effect, and to assess the risks of the drug, thereby enabling a benefit-risk comparison and  
appropriate labeling.

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The statutory requirement for marketing approval is “substantial evidence” that the drug will  
have its claimed effect.<sup>15</sup> This requirement is the same for common and rare diseases.  
Substantial evidence is based on the results of adequate and well-controlled investigations.<sup>16</sup>  
Adequate and well-controlled studies are defined as studies that are designed and conducted such  
that they 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.”<sup>17</sup> Many years of  
scientific and medical experience have established essential elements that determine whether a  
study is adequate and well-controlled, and these characteristics are both required by regulation  
and generally recognized and accepted by the scientific community. Design features of an  
adequate and well-controlled study must include:<sup>18</sup>

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<sup>15</sup> Section 505(d) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(d))

<sup>16</sup> In some circumstances, data from one adequate and well-controlled clinical investigation and confirmatory evidence are sufficient. See section 505(d) of the FD&C Act and References, including the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*.

<sup>17</sup> 21 CFR 314.126

<sup>18</sup> *Ibid.*

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- 456 • A clear statement of the study objectives.  
457
- 458 • A design that permits a valid comparison with a control. Controls may be concurrent  
459 (e.g., placebo, no-treatment, active treatment, dose comparison) or, in limited and special  
460 circumstances, historical.  
461
- 462 • Methods of patient selection that are well-defined and result in the selection of an  
463 appropriate population for study.  
464
- 465 • Methods that minimize bias in assigning patients to study groups and ensure  
466 comparability between study groups (e.g., randomization).  
467
- 468 • Methods that minimize bias in study conduct, outcome measures, and analysis (e.g.,  
469 blinding techniques).  
470
- 471 • Methods of assessment of patients' response that are well defined and reliable (e.g.,  
472 appropriate endpoints for the study objectives).  
473
- 474 • Methods of analysis adequate to assess effects of treatment (e.g., an appropriate statistical  
475 analysis plan).  
476

477 These design features should be prospectively specified and included in the investigational plan  
478 (e.g., study protocol) with sufficient details of study design, conduct, and analysis to allow  
479 critical evaluation and determination of whether the characteristics of an adequate and well-  
480 controlled study are present. Internationally recognized principles for the conduct of clinical  
481 studies are published,<sup>19</sup> and sponsors are urged to consult these resources throughout drug  
482 development.  
483

484 Assessment of the safety of the drug should use “all tests reasonably applicable” to establish  
485 safety for its intended use.<sup>20</sup> Clinical trials should also include a monitoring plan adequate to  
486 ensure the safety of clinical trial patients. The elements and procedures of the monitoring plan  
487 should be based upon what is known about the drug, including nonclinical toxicology and  
488 chemistry, manufacturing, and controls (CMC) information, and, if available, previous human  
489 experience.  
490

491 There is no specific minimum number of patients that should be studied to establish effectiveness  
492 and safety of a treatment for any rare disease. The number of patients to establish effectiveness  
493 and safety is determined on a case-by-case basis, taking into consideration the persuasiveness of  
494 the data (e.g., comprehensiveness and quality), the nature of the benefit provided (or expected in  
495 the case of surrogate endpoints), the length of treatment or exposure, the patient population that  
496 would be treated after marketing approval, and the concern for potential of harm from the

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<sup>19</sup> See References, including the ICH guidances for industry *E9 Statistical Principles for Clinical Trials* and *E10 Choice of Control Group and Related Issues in Clinical Trials*.

<sup>20</sup> See References, including the reviewer guidance *Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review*.

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497 treatment. Treatment duration should also be appropriate for the disease under study (e.g.,  
498 chronic as compared to acute conditions). When conducting a benefit-risk assessment for a drug  
499 for a serious or life-threatening illness, FDA also recognizes that greater risks may be accepted  
500 for a treatment that is an advantage over available therapy.<sup>21</sup> This reflects FDA’s commitment to  
501 expediting the availability of drugs for serious diseases as soon as it can be concluded that the  
502 benefits of the drugs exceed their risks, while preserving appropriate standards for safety and  
503 effectiveness, especially when these patients have unmet needs, as is often the case with patients  
504 with rare diseases.

505  
506 Clinical trial plans should ensure that data are collected and recorded in an accurate way.  
507 Sponsors should conform to internationally accepted scientific quality principles for recording  
508 and reporting trials to assure that clinical trial data are credible. Ethical principles for the  
509 conduct of clinical trials are described in international guidelines and agreements such as the  
510 ICH guidance for industry *E6 Good Clinical Practice: Consolidated Guidance*. In addition to  
511 ensuring the safety and rights of human subjects participating in clinical trials,<sup>22</sup> FDA’s oversight  
512 of clinical investigations provides assurance that the quality of scientific investigations of a drug  
513 is adequate to permit an evaluation of the benefits and risks of the drug, and that the data  
514 generated from these investigations can meet statutory standard for marketing approval.

515  
516 The investigational plan and content of applications for approval of new drugs can vary widely  
517 depending on the drug and disease under study.<sup>23,24</sup> FDA recognizes that the investigation of  
518 potential drugs for the treatment of rare diseases is challenging, and study approaches used in  
519 common diseases are not always feasible for rare diseases. Sponsors should meet early with  
520 FDA to identify clinical trial designs that are feasible for the patient population and disease  
521 under study, and that will have sufficient scientific rigor to meet the standards for adequate and  
522 well-controlled investigations. Given the complexity of drug development for rare diseases,  
523 FDA encourages frequent communication throughout drug development.

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### **VIII. CHEMISTRY, MANUFACTURING, AND CONTROLS**

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528 Manufacturing of drugs for both rare and common diseases typically undergoes development in  
529 parallel with clinical development. FDA encourages sponsors to discuss their CMC  
530 development plans early (such as at pre-IND meetings) and throughout drug development to  
531 decrease the potential for developmental or approval delays related to drug manufacturing.

532

533 As drug development proceeds to later-phase studies, factors such as increasing experience with  
534 manufacture of the drug, changes in available technology, and the need for larger amounts of the  
535 drug in later phases of clinical development may lead to manufacturing changes that include

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<sup>21</sup> 21 CFR 312.84, subpart E

<sup>22</sup> 21 CFR part 50, Protection of Human Subjects; 21 CFR part 56, Institutional Review Boards

<sup>23</sup> 21 CFR 312.80 and 21 CFR 314.105

<sup>24</sup> See References, including the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*.



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536 manufacturing procedures, purification methods, and increased scale. FDA also recognizes that  
537 transfer of manufacturing responsibilities may occur after initial testing (e.g., from a single  
538 investigator to a company, or a small company to a larger one), which may be a particular  
539 consideration for rare disease drugs. Any of these changes (even changes expected to be minor)  
540 might result in unanticipated changes to drug characteristics (e.g., drug impurities and physical-  
541 chemical characteristics of proteins). If significant differences are identified in drug  
542 characteristics after a manufacturing change compared to drug batches used in earlier nonclinical  
543 or clinical studies, then additional nonclinical and clinical studies may be needed because these  
544 differences raise concerns that the knowledge gained will not apply to further use of the drug.  
545 Examples of some of the many ways a change in drug characteristics may adversely affect drug  
546 development include the following:

- 547  
548 • Changes in the amount or type of impurities compared to batches used in toxicology  
549 studies might raise concerns that the drug used in later clinical studies has unknown  
550 toxicological characteristics. In some cases this concern can only be addressed with  
551 additional toxicology studies evaluating the newly produced drug, delaying the clinical  
552 development program.
- 553  
554 • Product characteristic changes in the planned commercial drug after the end of clinical  
555 studies might raise concern that the effectiveness and safety findings of the clinical  
556 studies do not apply to the newly manufactured drug. This could warrant additional  
557 studies (nonclinical, clinical, or both) to address the concern before marketing approval.

558  
559 FDA recommends that sponsors consider the potential development of the manufacturing  
560 process in the entire drug development program early, including which nonclinical and clinical  
561 studies are intended to be conducted with each change in the manufacturing process, and whether  
562 bridging studies will be needed. Sponsors should design adequate testing procedures early and  
563 implement them in a timely manner to mitigate delays. Changes in the manufacturing process  
564 should be implemented as early as feasible to decrease the potential for delay-causing drug  
565 differences or, if there are differences, to allow time to evaluate their effects. Given the wide  
566 variety of drugs, some of which are complex, FDA advises sponsors to consult existing  
567 manufacturing guidances (see References for a list of selected guidances; consult the FDA Web  
568 site for other pertinent guidances).

569

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<sup>25</sup> When final, this guidance will represent the FDA’s current thinking on this topic.

<sup>26</sup> When final, this guidance will represent the FDA’s current thinking on this topic.

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