ACRP Regulatory Affairs Committee Review of FDA Draft Guidance

Rare Diseases: Common Issues in Drug Development

What is the guidance?
This draft guidance is intended to support sponsors that are developing drug and/or biological products intended to treat rare diseases by providing guidance on selected issues that are common among drug development for rare diseases.

Who does it impact & how?
The primary impact is on Sponsors at the program and protocol development level.

What did ACRP RAC have to say about it?
The Regulatory Affairs Committee commented that the current state of the draft guidance appears burdensome to Sponsors and may actually discourage developing drugs for rare diseases and is contradictory to the Orphan Drug Act which indicates that "changes would need to be made in the applicable Federal laws to reduce the costs of developing such drugs and provide financial incentives for the development of orphan drugs." ACRP provided many comments to support this overall sentiment.

When were the RAC's comments sent to the agency?
October 16, 2015

Where can I access this document?
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM458485.pdf

ACRP
ASSOCIATION OF CLINICAL RESEARCH PROFESSIONALS

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ACRP promotes excellence in clinical research.

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October 16, 2015

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

In reference to docket number: **FDA-2015-D-2818-0001**

The Association of Clinical Research Professionals (ACRP) is the primary resource for clinical research professionals in the pharmaceutical, biotechnology and medical device industries, and those in hospital, academic medical centers and physician office settings. ACRP was founded in 1976 to address the educational and networking needs of research nurses and others who supported the work of clinical investigations. Almost 40 years later, ACRP is a global association comprised of individuals dedicated to clinical research and development. Our mission is "ACRP promotes excellence in clinical research." The Academy of Physicians in Clinical Research (APCR) is an affiliate of ACRP and is the leading professional organization, exclusive to physicians, that supports and addresses these unique issues and challenges of all physicians involved in clinical research.

ACRP appreciates the opportunity to provide the FDA with our comments on the Rare Diseases: Common Issues in Drug Development draft guidance as this issue has a significant impact on our membership.

We are concerned that this guidance in its current draft state places additional burden on Sponsors and may further discourage Sponsors from developing drugs for rare diseases and is contradictory to the Orphan Drug Act which indicates that "changes would need to be made in the applicable Federal laws to reduce the costs of developing such drugs and provide financial incentives to develop such drugs" and that "it is in the public interest to provide such changes and incentives for the development of orphan drugs." The attached document provides detailed comments/suggestions/recommendations on specific sections of the draft guidance.

ACRP hopes that our feedback helps the FDA improve the final version of the document or decide potentially to withdraw this draft guidance because the document does not support the Orphan Drug Act and does not seem to serve the patients who have these rare diseases and who desperately need and want new options (sometimes just to survive). The guidance in its current draft does not encourage the use of patient panels and advocacy groups in the development of drugs to treat rare diseases, which are most often the groups with the access to patients, health literacy and disease burden

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awareness and could be instrumental in rare disease drug development. We would therefore welcome further discussion with the Agency on this. These patients are quite likely willing to take the added risk of an "unproven" medication especially in a well-controlled study because they have no other options. ACRP is concerned that this guidance may in fact deter development of drugs for rare diseases in the United States and result in US patients traveling to foreign countries to seek treatment options.

Please let me know if you have any questions regarding our comments, or if we may otherwise serve as a resource on issues related to clinical research.

Sincerely,

Jim Kremidas
Executive Director

FDA-2015-D-2818-0001 :Rare Diseases: Common Issues in Drug Development			
Page Number	**Text Line**	**Reference** *(if applicable)*	**Comments**
1-2	28-42; 66-67	Introduction & Background	The draft guidance states "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 • Reliable endpoints and outcome assessment • Standard of evidence to establish safety and effectiveness • Drug manufacturing considerations during drug development" AND "...FDA acknowledges that certain aspects of drug development that are feasible for common diseases may not be feasible for rare diseases." Rare diseases inherently have insufficient information about the disease. The FDA's statements within the draft guidance regarding natural history studies are perceived as additional requirements and added burden on pharmaceutical manufacturers as these studies, which, from our understanding, are not necessarily designed for studying patient safety or drug efficacy, but rather to gain a better understanding of the disease process(es). We are concerned that this places undue burden on pharmaceutical manufacturers and would further delay the ability to provide drugs to potentially serve those with a rare disease.
3	92-112	Section III. Natural History Studies	The types of "In-depth understanding" goals listed on page 3 are interesting but not typically plausible or related directly to development of a new drug (e.g. understanding the "full range of disease" and identifying "subpopulations" are particularly problematic with rare diseases and these types of details are not typically required of other drugs manufacturers who are certainly held to defining the appropriate indication for use in the group they have determined to treat – these companies do not and probably should not typically have the responsibility to define all patients in all subtypes when their drug is not designed for those other groups and subgroups). Typically rare disease groups are not readily split into "subpopulations" with any

			statistical confidence until years of study have occurred and we do not believe patients should suffer in silence while waiting for this type of "nice to have" data. That being said, we believe that the industry and our government have a responsibility to help fund such studies to better understand the diseases.
3	105-107; 116-127	Section III. Natural History Studies	In order to clinically characterize the progression of a rare disease and define its natural history, this guidance should encourage sponsors to fully engage the rare patient community to support parameters for understanding the timing of symptoms of disease progression, based on current medical management practices, including a broader understanding of issues that arise from comorbidities and issues related to access to care. There is precedent for successful relationships between industry stakeholders and patient advocacy groups to draft guidance. For the first time, the development of FDA draft guidance "Duchenne Muscular Dystrophy and Related Dystrophinopathies: Developing Drugs for Treatment" (in June 2015) was preceded by the submission of a draft by an independent Duchenne Muscular Dystrophy disease advocacy group: http://www.parentprojectmd.org/site/PageServer?pagename=Advocate_fdaguidance and http://www.fda.gov/Drugs/DrugSafety/ucm448894.htm. Based on this successful model established by FDA, it suggests that sponsors could benefit from working with disease therapeutic groups to understand natural history and design patient reported outcomes that reflect patient disease burden.
4	162-164	Section III. Natural History Studies	The FDA seems to suggest they will no longer allow the use of "historical comparators." In the setting of rare diseases, this could be catastrophic to the development of new drugs since the cost and time to do head to head randomized controlled trials may be prohibitive simply due to the fact that the patients may not actually exist in the world (especially if every sub-group must be detailed and defined – each sub-group may be really small number of individuals). Can the Agency please clarify if historical comparators will continue to be acceptable controls?
3, 5-6	109-112 167-235	Section IV. Disease Pathophysiology and	We find the reference to development of "new or optimized biomarkers" inappropriate in this particular guidance document intended for rare diseases and suggest that this requirement be removed. The added burden for full scale biomarker development to meet FDAs processes in this particular "biomarker" area does not seem to be in scope for a rare disease drug

		Identification and Use of Biomarkers	development program which should, we hope, be designed to provide "incentives associated with orphan-drug designation to make developing drugs for small numbers of patients financially viable" as stated in the Orphan Drug Act.
4	173-174	Section IV. Disease Pathophysiology and Identification and Use of Biomarkers	Grammatical error: "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:" Consider revising "how it is clinically manifest over time" to "how it clinically manifests over time".
13	519-523	Section VII. Evidence of Effectiveness and Safety	"Sponsors should meet early with FDA to identify clinical trial designs that are feasible for the patient population and disease under study, and that will have sufficient scientific rigor to meet the standards for adequate and well-controlled investigations. Given the complexity of drug development for rare diseases, FDA encourages frequent communication throughout drug development." At no point does this guidance express that sponsors should be meeting with patient disease advocacy groups to assess feasibility of drug development or protocol feasibility. For aforementioned reasons, this may be recommended and we encourage the Agency to include language to this effect in the guidance document.
15-16	570-635	References	The list of references is an overwhelming list and perceived as a further deterrent to pursuing development of drugs to treat rare diseases. We suggest that this list be re-organized by topic with the goal of having fewer references for particular topical areas or pared down altogether.

Rare Diseases: Common Issues in Drug Development

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Jonathan Goldsmith at 240-402-9959, or (CBER) Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010.

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

August 2015
Rare Diseases

Rare Diseases: Common Issues in Drug Development

Guidance for Industry

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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

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Rare Diseases: Common Issues in Drug Development Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not 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[2] 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.[3] 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

[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 (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) 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.

[3] 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.

- 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[4] 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).[5] 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.[6] 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

[4] Ibid.

[5] 21 CFR 314.126

[6] 21 CFR 314.105

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

III. NATURAL HISTORY STUDIES

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

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

- Defining the disease population, including a description of the full range of disease manifestations and identification of important disease subtypes

- Understanding and implementation of critical elements in clinical study design, such as study duration and choice of subpopulations

- Developing and selecting outcome measures that are more specific or sensitive to changes in the manifestations of the disease or more quickly demonstrate safety or efficacy than existing measures.

- Developing new or optimized biomarkers that may provide proof-of-concept (POC) information, guide dose selection, allow early recognition of safety concerns, or provide supportive evidence of efficacy. In some cases, biomarkers can be used for surrogate endpoints.[7]

No single set of data elements adequately describes all rare diseases. Rare diseases are highly diverse and as a group affect many organ systems with wide variations in the rates and patterns of manifestations and progression. Selection of the data elements to collect in a natural history study should be broad and based on features of the disease, including morbidities 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, even if not serious aspects of the

[7] See References, including the guidance for industry *Expedited Programs for Serious Conditions — Drugs and Biologics.*

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

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

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

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

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

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.

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

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

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

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

V. NONCLINICAL STUDIES

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

[8] 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.

[9] 21 CFR 312.23(a)(8)

[10] Ibid.

Sponsors should base toxicology study design on the biology of the disease, expected pharmacology of the drug, existing POC data, clinical trial design or designs to be proposed, and the indication being sought. Healthy animals generally are the test system used in traditional toxicology testing and, in most circumstances, should be the test system used to support clinical trials. Internationally accepted, general guidances are available for the timing and nature of nonclinical safety studies relative to clinical trials in drug development.[11] These guidances also describe potential areas of FDA flexibility in determining the nonclinical data necessary to support an evolving clinical development program. Among the factors FDA considers are the design and objectives of the proposed clinical investigations, the existing accumulated nonclinical and human data and experience with the drug, and the possible risks to humans. Information from previous nonclinical and human use has the potential to decrease the amount of new toxicology data needed. Factors such as drug constituents, dosage form, route, and dose and regimen of administration may be considered in determining the relevance of prior data. FDA also considers the diverse biology and structure of drugs and biologics (e.g., chemically synthesized drug products, recombinant protein products, plasma-derived products, cell therapy products, and gene therapy products)[12] in determining the nonclinical data necessary.

FDA may apply additional flexibility in evaluating development programs for drugs to treat serious and life-threatening disorders.[13] Under limited circumstances, clinical studies can proceed in the absence of standard toxicology studies; however, this approach should be well justified and is only appropriate for serious or life-threatening diseases where current treatments, if any, are inadequate. In these circumstances, we strongly recommend that sponsors meet with FDA before starting animal studies to obtain concurrence with an abbreviated nonclinical program that can support the proposed clinical trials.

When an animal model of the disease is available, pharmacology studies may contribute to understanding the actions of the drug on disease pathophysiology and guide plans for measuring biological effects in patients. Toxicology testing in an animal model might be performed, but usually will not substitute for all toxicology testing in healthy animals because of concern that the disease pathophysiology may obscure some drug toxicity. Safety evaluation in an animal model also may be particularly valuable when it is suspected that drug toxicity may be more severe in the presence of disease pathophysiology.

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[11] 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.

[12] 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.

[13] 21 CFR 312.80, subpart E

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

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

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

VI. EFFICACY ENDPOINTS

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

Endpoint selection for a clinical trial entails multiple considerations including:

- An understanding of the disease, including the likelihood, range, and course of clinical manifestations associated with the disease (disease definition). Sponsors can often obtain this knowledge, along with disease characteristics of patient subsets, from a natural history study of the disease (see section III, Natural History Studies).

[14] 21 CFR 312.42(b)

- An understanding of the clinical characteristics (manifestations and timing) of the specific population targeted by the drug (which may be a subset of the total population with a disease).

- An understanding of which aspects of the disease are meaningful to the patient and might also be affected by the drug's activity. This evaluation is influenced by knowledge of the pathophysiology of the disease and prior experience (if any) with the drug or related drugs, including nonclinical and clinical effects and pharmacology.

- Knowledge of what patient assessments exist or might be refined or developed for use as outcome assessment tools to measure selected aspects of the disease.

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

- Validity, that is, how well scores used to define a study endpoint represent the selected aspects of the disease reflected in the objectives of the clinical trial.

- Reliability, including inter-rater and intra-rater (test-retest) reliability. Reliability is especially important when clinical trials assess small numbers of patients.

- Feasibility, including expense, tolerability, and availability of any specialized equipment or skills necessary to perform the assessment. For example, rare disease clinical trials are often conducted at a small number of centers that have the appropriate specialized equipment, and long travel distances for patients may be a barrier. In other cases, complex patient assessments capable of detecting small changes may rely upon procedures that are difficult and poorly accepted by the patient. Both may hinder patient enrollment or completeness of study visits.

- Resistance to bias. Although treatment-assignment blinding is important to lessening the potential for bias in study results, ensuring perfect blinding is difficult for many treatments. An assessment that is less readily influenced by a patient's or investigator's knowledge of treatment assignment can improve confidence in the study results.

- Ability to detect change. Assessments that are more finely detailed, with commensurate reliability, may offer the potential to detect smaller changes in a disease manifestation that it is intended to measure (i.e., the potential for greater sensitivity to clinical effects).

- Relationship to meaningful symptoms or function. Some assessments directly measure the symptoms or functional abilities that are important to understand treatment benefit in the patient with the disease of interest. Other assessments, such as clinical outcome assessments and certain biomarkers used as surrogate endpoints do not directly measure these but are used to predict clinical benefit. This relationship should be taken into consideration.

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

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

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

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

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

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

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

VII. EVIDENCE OF EFFECTIVENESS AND SAFETY

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.

The statutory requirement for marketing approval is "substantial evidence" that the drug will have its claimed effect.[15] This requirement is the same for common and rare diseases. Substantial evidence is based on the results of adequate and well-controlled investigations.[16] 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."[17] 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:[18]

[15] Section 505(d) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(d))

[16] 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.*

[17] 21 CFR 314.126

[18] Ibid.

- A clear statement of the study objectives.

- A design that permits a valid comparison with a control. Controls may be concurrent (e.g., placebo, no-treatment, 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 study.

- Methods that minimize bias in assigning patients to study groups and ensure comparability between study groups (e.g., randomization).

- Methods that minimize bias in study conduct, outcome measures, and analysis (e.g., blinding techniques).

- Methods of assessment of patients' response that are well defined and reliable (e.g., appropriate endpoints for the study objectives).

- Methods of analysis adequate to assess effects of treatment (e.g., an appropriate statistical analysis plan).

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

Assessment of the safety of the drug should use "all tests reasonably applicable" to establish safety for its intended use.[20] Clinical trials should also include a monitoring plan adequate to ensure the safety of clinical trial patients. The elements and procedures of the monitoring plan should be based upon what is known about the drug, including nonclinical toxicology and chemistry, manufacturing, and controls (CMC) information, and, if available, previous human experience.

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

[19] 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*.

[20] See References, including the reviewer guidance *Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review*.

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

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

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

VIII. CHEMISTRY, MANUFACTURING, AND CONTROLS

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

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

[21] 21 CFR 312.84, subpart E

[22] 21 CFR part 50, Protection of Human Subjects; 21 CFR part 56, Institutional Review Boards

[23] 21 CFR 312.80 and 21 CFR 314.105

[24] See References, including the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.*

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

- Changes in the amount or type of impurities compared to batches used in toxicology studies might raise concerns that the drug used in later clinical studies has unknown toxicological characteristics. In some cases this concern can only be addressed with additional toxicology studies evaluating the newly produced drug, delaying the clinical development program.

- Product characteristic changes in the planned commercial drug after the end of clinical studies might raise concern that the effectiveness and safety findings of the clinical studies do not apply to the newly manufactured drug. This could warrant additional studies (nonclinical, clinical, or both) to address the concern before marketing approval.

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

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