

Special Trial Design Considerations in Rare Disease Trials

Patroula Smpokou, MD, FACMG

Clinical team leader

Division of Gastroenterology and Inborn Errors Products

Office of New Drugs/ CDER/ FDA

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Disclaimer

The views expressed in this presentation are my own and do not represent an official FDA position.

I have no financial interests to disclose.

Learning Objectives

- Provide important regulatory definitions of rare diseases and orphan products
- Outline the regulatory framework for drug evaluation and approval and its application to rare disease drugs
- Summarize special programs in rare disease drug development
- Highlight special trial design considerations in rare disease drug development programs

Definitions

- Rare disease = disease (condition) affecting < 200,000 people in the U.S.
- Orphan drug (product) = drug intended to treat a rare (orphan) disease
- Orphan Drug Designation (ODD) criteria
 - Investigational product must be intended to treat a rare disease
 - Adequate demonstration of a medical plausibility for the drug's expected benefit

or

 - A product for which there is no “reasonable expectation” that the development costs would be recovered from U.S. sales

U.S. Evidentiary Standard for Drug Approval



- 1962 Drug Amendments to the Food, Drug & Cosmetic Act (FD&CA) require:
 - establishment of effectiveness as a prerequisite for marketing approval
 - effectiveness is established by “**substantial evidence**”
 - Section 505(d) of the FD&C Act:

“Evidence consisting of **adequate and well- controlled investigations**, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that **the drug will have the effect it purports or is represented to have** under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.”

Adequate & Well-Controlled Studies

21 CFR 314.126



- Traditionally a minimum of 2 adequate and well-controlled studies (each persuasive on its own)
- 1997: FDA Modernization Act (FDAMA) provided a complimentary statutory standard for demonstration of substantial evidence of effectiveness
 - **one adequate and well-controlled study and “confirmatory” evidence**

Adequate and Well-Controlled Studies

- Studies that have been designed well enough so as to be able **“to distinguish the effect of a drug from other influences, such as spontaneous change, placebo effect, or biased observation”** (21 CFR 314.126)
- Adequate and well-controlled studies have:
 - Clear statement of purpose
 - Appropriate control for valid comparison
 - Appropriate selection of subjects
 - Appropriate assignment of subjects to treatment and control
 - Adequate measures to minimize bias
 - Well-defined and reliable methods of assessing response
 - Prospectively planned analyses designed with rigor

Application of regulatory standards to rare disease drug approval



- Regulations recognize need for flexibility

21 CFR 314.105(c)

- “While the statutory standards apply to all drugs, the many kinds of drugs that are subject to the statutory standards and the wide range of uses for those drugs **demand flexibility in applying the standards**”
- “The FDA is required to **exercise its scientific judgment** to determine the **kind and quantity of data**....required to provide for a particular drug to meet the statutory standards.”

Special regulatory programs in rare diseases



- Orphan drug designation
- Rare pediatric disease designation
 - Rare pediatric disease priority review voucher
- Expedited Programs
 - Fast track designation
 - Breakthrough designation
 - Accelerated approval
 - Priority review



Use of FDA Approval “Flexibility”

FDA Novel Drug and Biologic Approvals 2006 - 2017
(n = 423)

	Orphan Drug	non-Orphan
2 or more Adequate and well-controlled studies	35%	74%
1 adequate and well-controlled study plus supporting evidence	60%	25%
Other: no adequate and well-controlled study, or atypical program	4%	2%
Accelerated Approval	25%	3%
Regular Approval	75%	97%
“Conventional” Approval (Regular approval based on 2+ AWC studies)	29%	72%
“Flexible” Approval (Accelerated approval and/or approval based on <2 AWC studies)	71%	28%

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Trial design: Special Considerations in Rare Diseases

1. Natural history knowledge
2. Controls/ Randomization
3. Trial population
4. Dose finding
5. Endpoints/ Statistical planning

1

Disease Natural History

Natural history studies in rare diseases



- Track natural disease course over time
- Identify variables that correlate with disease and outcomes in the absence of treatment
- Generate information on:
 - Genotypic and phenotypic variation (disease subtypes, population subsets)
 - Genotype-phenotype associations
 - Disease course, rate of progression (e.g. chronic vs episodic symptoms)
 - Major morbidities
 - Cause(s) of early mortality
 - Variables that correlate with disease severity, specific symptoms, clinical outcomes (e.g. biomarkers)
 - Relevant and meaningful clinical outcome assessments (COAs)

Importance of natural history knowledge



- Informs trial design for selection of:
 - Appropriate patient population/subpopulations
 - Most informative trial design
 - Sufficient trial duration to observe change in selected outcomes
 - Reliable, disease-specific biomarkers for population selection, patient stratification, assessment of pharmacodynamic changes in response to treatment
 - Relevant and clinically meaningful efficacy endpoints

Natural history in rare diseases

- Incomplete NH knowledge
 - Lack of robust, prospective, longitudinal data
 - cross-sectional studies, case reports/series, retrospective studies are easier, less expensive, faster to conduct
 - slowly progressive symptoms over decades
 - limited patient numbers/datapoints
 - Disease heterogeneity
 - phenotypic- variable age of onset, different disease progression rate, variable manifestations among affected patients and in children vs adults
 - genotypic- different gene variants, variants/polymorphisms in other genes or epigenetic changes can affect phenotypic expression, different disease severity
- Assessments in NH studies typically not designed for eventual regulatory use (if needed), e.g. historical control

Natural History Studies as Historical Controls

- “Infrequent” use of NH studies
 - “usually reserved for special circumstances”⁴
 - Objective endpoint (mortality), large treatment effect
 - more frequent in rare diseases than in common diseases
- Historical control limitations:
 - Different baseline characteristics, alternative treatments (confounding- known and unknown variables)
 - Different instruments used to assess outcomes, different assessment frequencies/assessors (bias)
 - Retrospectively collected data with critical limitations
 - Inadequate documentation, missing data
 - Potentially more severely affected patients in NH studies (“healthier” populations tend to participate in clinical trials)
 - Comparability of populations?

⁴21CFR314.126 Adequate and well-controlled studies

Natural History Studies as Historical Controls



- If a natural history external control group is proposed, it should be ideally identified prospectively to ensure comparability to treatment group
 - Natural history external control group created *post hoc* is very difficult to interpret (unless effect of test drug is large) due to known and unknown confounding
- In many cases, randomized controlled clinical trials remain the fastest way to determine effectiveness:
 - Randomize as early as possible in development to avoid potentially misleading and uninterpretable findings from open-label trials
 - Employ methods to limit time on placebo (e.g., dose-response, delayed start, randomized withdrawal, interim analysis)

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Controls/ Randomization

Controls

- Control group is fundamental for valid comparative assessment of outcome variables (safety, PD, efficacy)
- Types: concurrent vs non-concurrent
 - placebo control
 - no treatment, standard-of-care (SOC) treatment control
 - active control (e.g. other drug approved for disease)
 - historical control (group of untreated patients followed in the past)

Randomization

- Subjects randomly assigned to groups through specific algorithm/process
- Ensures that compared groups are balanced on both known and unknown factors (confounders)
-if sample size is sufficient
- Foundation of inferential statistics

Randomization in rare disease trials

- If sample size is small, randomization may not ensure balanced groups
- Placebo-controlled, randomized trials
 - patient/family hesitancy
 - potential ethical considerations (severe, rapidly progressive diseases)

3

Trial Population

Population in rare disease trials

- Childhood-onset diseases
- In the most severe forms, only children are available/
target population (not survive to adulthood)
- Differences in clinical symptoms, severity, and disease trajectory in children vs adults with same rare disease
- Subgroups within same rare disease with differences in disease trajectory, symptomatology, symptom severity

“Additional Safeguards for Children in Clinical Investigations”

(21 CFR 50, subpart D)



Research involving children must either:

a. present “minimal” risk or a “minor increase over minimal” risk absent a potential for direct benefit to each enrolled child (21 CFR 50.51/53)

OR

b. **provide the prospect of direct (clinical) benefit** to each child if the risks are more than a minor increase over minimal risk, **the risks must be justified by the anticipated benefit**, and the **anticipated benefit-risk assessment must be at least as favorable** as any accepted alternative treatments (21 CFR 50.52)

Prospect of Direct Benefit (PDB)

21 CFR 50.52

- A “**direct**” benefit may improve the health or well-being of each individual child and results from the research intervention (drug) being studied
 - not from other interventions included in protocol (blood draws, imaging, other)
- What is the available evidence (either from adult patients or animal models) about the anticipated clinical effects of the intervention (drug)?
 - Does the available data make us reasonably comfortable that children might directly benefit from the drug?
 - Are the dose and duration of treatment with the drug appropriate/sufficient to offer the anticipated benefit?
 - For diagnostic procedures, would the procedure normally be done as part of routine clinical care? Would the data impact clinical care?

“First-in-Children” Trial

21 CFR 50.52

- Can one infer a sufficient prospect of direct benefit from animal studies alone to justify a “first-in-children” clinical trial?
 - the data necessary to establish a sufficient prospect of direct benefit (PDB) to justify the risks of product administration varies with the severity of the disease and the adequacy of alternative treatments
- Potential evidence supporting PDB:
 - Drug structure (generally insufficient for PDB)
 - Drug function (based on mechanism of action)
 - Molecular target (receptor)
 - Biomarker (RNA/protein)
 - Pathophysiologic pathway (e.g. biochemical pathway in single gene disorders)
 - Animal disease model
 - Surrogate endpoints (e.g. disease-specific biomarker)
 - Clinical endpoints (e.g. disease manifestations, survival)

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Dose Finding

General preclinical dose finding

- Animal toxicology studies
 - What is the safety margin of the human dose from animal toxicology studies (NOAEL)?
 - Are expected toxicities able to be monitored and/or reversible?
 - Are there differences in the drug pharmacology between animals and humans ?

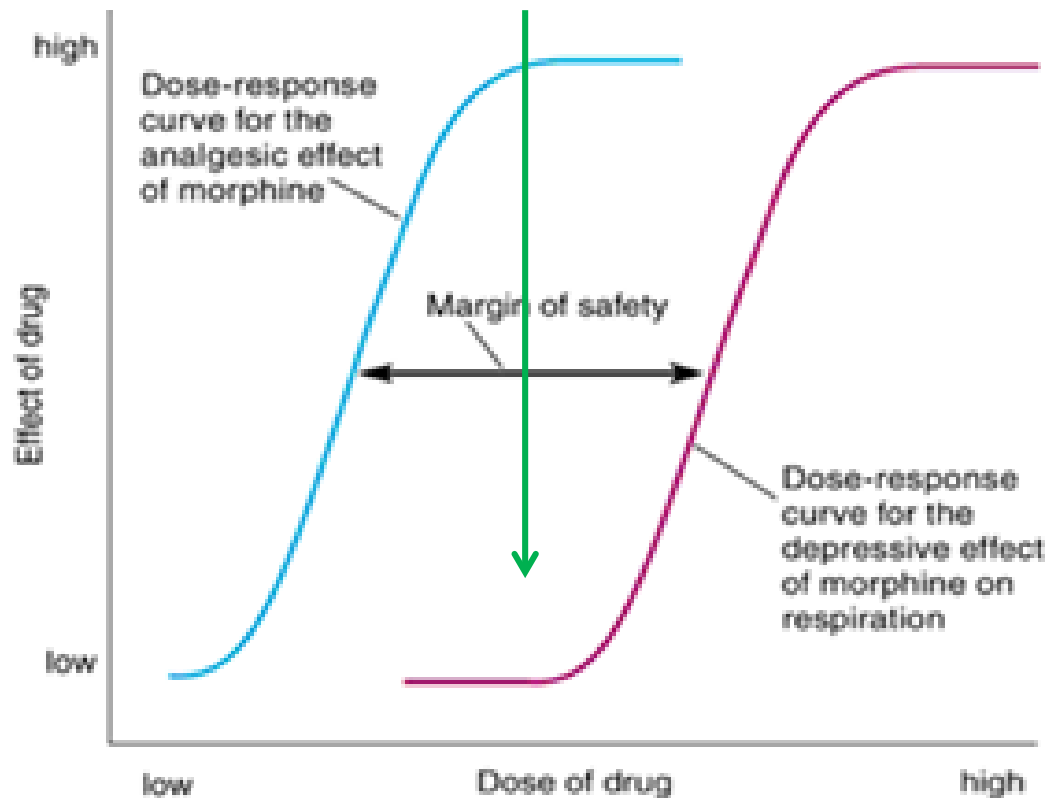
- Animal pharmacology studies
 - Characterize the relationship between dose, exposure, and biomarker changes in animal disease model
 - Efficacy study(ies) in animal disease model
 - Cross-species allometric scaling to derive initial human dose

- *In vitro* pharmacology studies
 - Assess biomarker(s) in cultured patient cells treated with drug

- Data on receptor binding affinity and receptor occupancy (RO) data to define target exposure(s) in humans

Traditional clinical dose finding

- “Optimal” dose = the most efficacious dose associated with minimal toxicity (or acceptable safety profile)
- “Optimal” dose selection depends on exposure-response (E-R) curves for efficacy and toxicity



Challenges in clinical dose finding in rare disease trials



- Serious diseases with shortened life expectancy
 - Urgency for new drug investigation and approval
 - Abbreviated development programs (costs)
- Small patient population/ few PK and PD data points
- Rapidly progressive phenotypes
 - Survival endpoints not useful for dose-finding
- Slower (not rapidly) progressive phenotypes
 - Lack of established clinical endpoints
 - Clinical endpoints require long duration for evaluation
 - Correlation of biomarker with clinical endpoints is unclear
- Lack of pharmacodynamic biomarker
- Lack of PK-PD correlation

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Endpoints/ Statistical Planning

Efficacy Endpoints: Measures of Clinical Benefit

- Clinical benefit = a positive effect on how an individual **feels, functions, or survives** (“clinically meaningful”)
- Measured through clinical outcome assessments (COAs)
 - Patient reported outcomes (PROs)
 - Clinician reported outcomes (ClinROs)
 - Observer reported outcomes (ObsROs)
 - Performance outcomes (PerfOs)
- Biomarker assessments do not measure clinical benefit
 - Do not assess how an individual feels, functions, or survives
 - Except: surrogate endpoints
 - “validated” surrogates for traditional approval vs “reasonably likely” surrogates for accelerated approval

Efficacy endpoints: rare disease trials



- Difficult to select given incomplete natural history knowledge
- No precedent/ regulatory experience with use of specific endpoints in a rare disease
- COAs often not studied (“validated”) in most rare diseases
- COAs often not sufficiently explored in early-phase trials
- May be different in children vs adults or among different subgroups with same rare disease
- For slowly progressive outcomes, short trial duration is insufficient to see observable changes
- Some may not be affected by drug based on MOA or due to insufficient penetration of the tissue (e.g. bone/cartilage)
- Patients may have completely different manifestations at baseline, e.g. primary mitochondrial diseases
 - Multiple primary endpoints?
 - Individualized endpoints?

General statistical considerations: rare disease trials

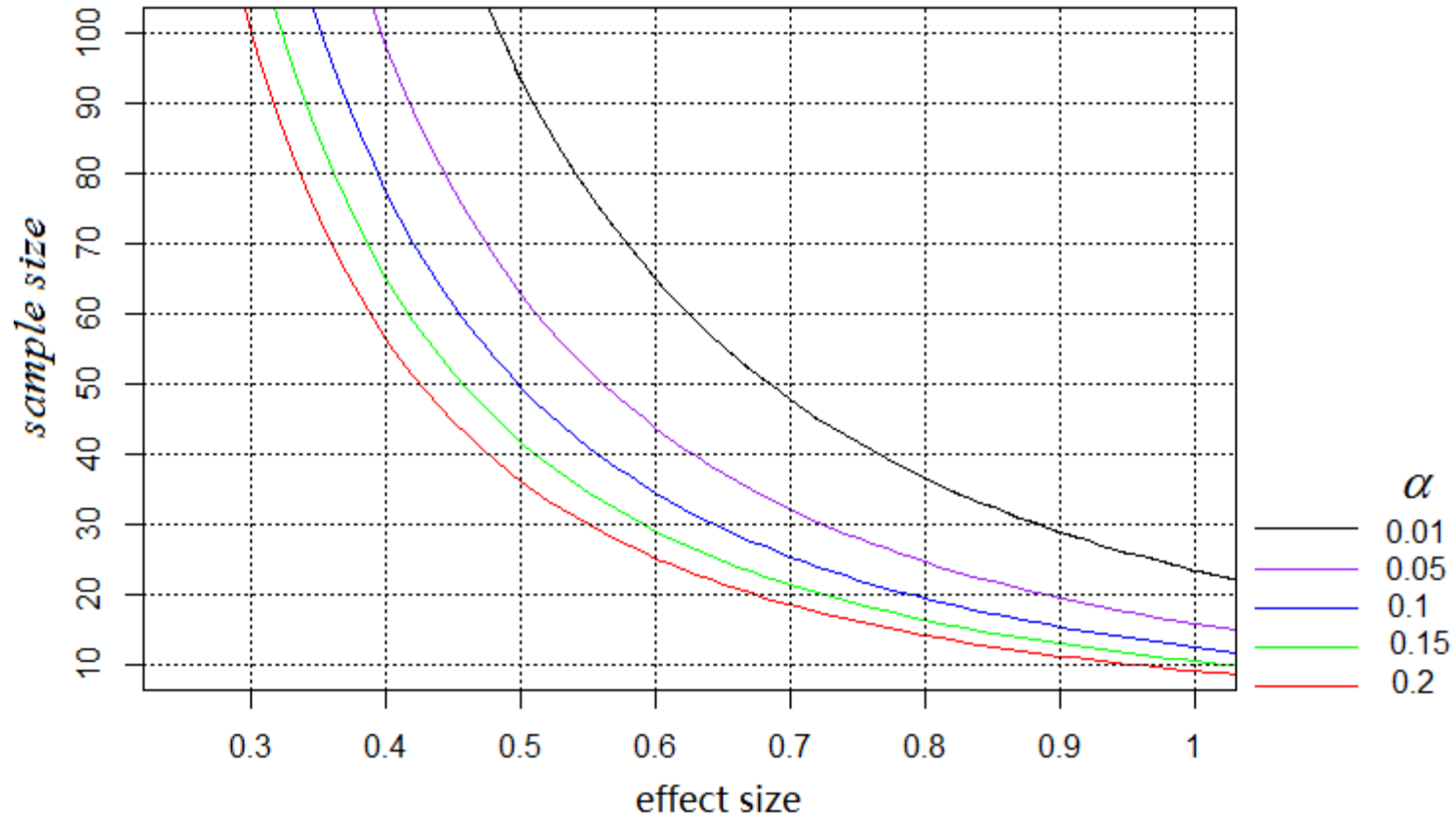


- Often insufficient study power, alpha considerations
 - Small sample size
 - Often small treatment effect size
- Endpoint selection/ hierarchy
 - Single primary endpoint vs multiple primary endpoints
 - Composite endpoint vs co-primary endpoints: A, B, C, D, or E vs A, B, C, D and E
 - Continuous vs binary endpoints
 - Survival endpoint (rare, not ethical)
- Statistical significance vs clinical meaningfulness of results
 - Often small treatment effects- difficult to interpret clinically

General Sample Size Considerations



(produced by Di Xiao; idea from John Doan quality control book)



- Assuming the study power is fixed, larger samples are needed when the effect size and/or **alpha** level are smaller
- If the effect size is fixed, to reduce the sample size, alpha level may need to be relaxed

Statistical Significance vs Clinical Meaningfulness

Trial for IBS	Mean (SD)	Mean difference from Placebo (97.5% CL)
Drug 250mg (3 times a day)	-1.4 (1.4)	-0.8 (-1.3, -0.3) [#]
Placebo	-0.6 (0.8)	

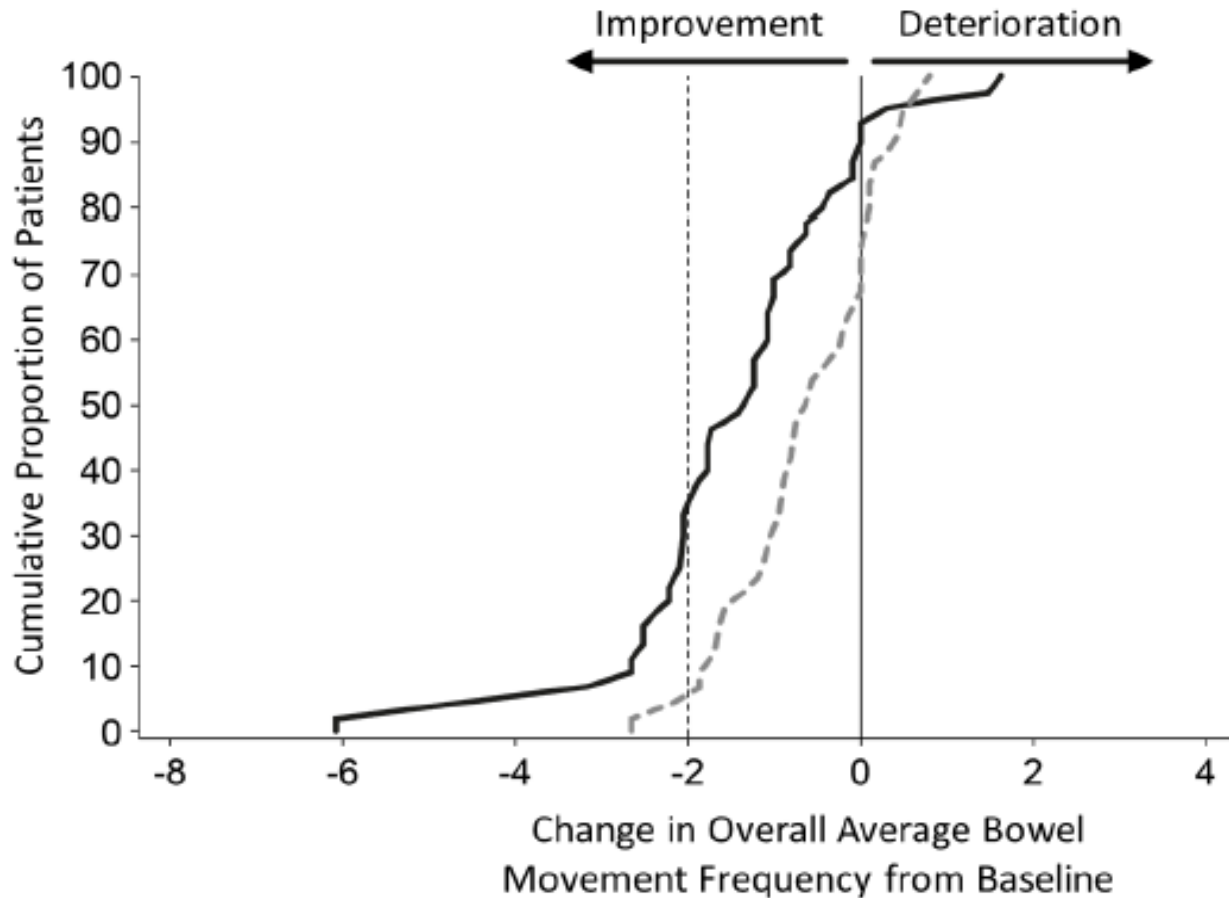
assessing change in bowel movements/day averaged over 12 weeks

$p < 0.001$

Assessing Clinical Meaningfulness



Figure 1: Cumulative Proportion of Patients with Carcinoid Syndrome Diarrhea Reporting Change in Overall Average Bowel Movement Frequency



*extracted from FDA label (solid line is for drug and dashed line for placebo)

Summary

- Knowledge of disease natural history is often lacking or incomplete in rare diseases
- Selection of the appropriate trial population can be challenging given phenotypic and genotypic heterogeneity
- Prospect of direct benefit (21 CFR 50.52) must be considered in trials enrolling children
- Randomization and appropriate controls are sometimes not used leading to difficult data interpretation and/or uninformative trials
- Dose exploration is often insufficient and dose selection may be partly based on preclinical data (toxicology/ pharmacology data in animals) in addition to human safety findings
- Selection of appropriate efficacy endpoints is often based on insufficient prior knowledge of performance characteristics of COAs and lack of robust natural history information
- Clinical interpretation of treatment effects is more difficult in rare disease trials where often the treatment effects are small

Question 1

To allow enrollment of children in a clinical trial of an investigational drug, the following regulatory criteria must be met:

- A. The drug must provide the prospect of direct (clinical) benefit to each individual child enrolled
- B. The drug-associated risks must be justified by the anticipated benefit
- C. The benefit-risk assessment must be at least as favorable as any accepted alternative treatments
- D. None of the above
- E. All of the above

Question 2

Dose selection in rare disease trials is often based on:

- A. Animal pharmacology and toxicology data
- B. Safety data in patients
- C. Efficacy data in patients
- D. A and B
- E. All of the above
- F. None of the above



Useful Resources

- FDA Guidance for Industry Rare Diseases: Common Issues in Drug Development (2019)
- FDA Guidance for Industry Rare Diseases: Natural History Studies for Drug Development (2019)
- FDA Guidance for Industry Rare Diseases: Early Drug Development and the Role of Pre-IND Meetings (2018)
- FDA Guidance for Industry Expedited Programs for Serious Conditions-Drugs and Biologics (2014)
- FDA Guidance for Industry Rare Pediatric Disease Priority Review Vouchers (2014)



Thank you

Questions/Comments:

patroula.smpokou@fda.hhs.gov

