REGULATORY FITNESS IN RARE DISEASE CLINICAL TRIALS

A Workshop by the
FDA's Center for Drug Evaluation & Research and
NIH's National Center for Advancing Translational Sciences

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WELCOME REMARKS

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SESSION 5: THE NUTS AND BOLTS OF INVESTIGATIONAL NEW DRUG (IND) APPLICATIONS AND ADDITIONAL CONSIDERATIONS

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U.S. FOOD & DRUG ADMINISTRATION

Understanding the Investigational New Drug (IND) Application Process

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Disclosure Statement

- This talk reflects the views of the authors
- This presentation is not intended to convey official US FDA or US government policy and no official support or endorsement should be inferred
- No conflicts of interest to disclose
- In this talk, “drug” refers to both drugs and biologics regulated by US FDA’s Center for Drug Evaluation and Research (CDER)

Investigational New Drug (IND)

- Federal law requires drugs pending marketing approval to be evaluated by FDA, prior to distribution or crossing state lines, unless meeting exemption criteria
- A Sponsor is a person or organization which initiates a clinical investigation with IND
- An Investigator is an individual who conducts clinical investigation(s)

21 CFR 312.3(b)

Topics

1. When to consider an IND and exemption criteria
2. Pre-IND considerations
3. IND Application: Content
4. IND Submission: The First 30 Days
5. Responsibilities of Sponsors and Investigators
6. IND Amendments
7. Reporting Requirements
8. Inactivation; Reactivation; Withdrawal; Termination
9. Tips for a Successful IND Application

When an IND is required

- Research involves a ***drug*** [section 201(g)(1) of Federal Food, Drug, and Cosmetic Act]
- Research is a ***clinical investigation*** [21 CFR 312.3]
- Clinical investigation is not exempt from IND requirements [21 CFR 312.3]

IND exemption criteria

- Drug is lawfully marketed in the US, and
- No intention of reporting to FDA a well-controlled study in support of new labeling indication or significant change in drug advertising, and
- No significant increase in risk, such as through administration route, dose, patient population, and
- If clinical investigation, conducted in compliance with IRB and with informed consent
- The investigation is not intended to promote or commercialize the drug product

IND exemptions

- Common examples:
  1. Approved marketed drugs
  2. Bioavailability or bioequivalence studies
  3. Clinical investigations with radioactive drugs considered safe for research
     - If uncertain whether an IND is required, submit your inquiry for our review

Guidance for Clinical Investigators, Sponsors, and IRBs: Investigational New Drug Applications (INDs) – Determining Whether Human Research Studies Can be Conducted Without an IND
https://www.fda.gov/media/79386/download

IND Types

- **Commercial**
- **Research**
  - Sponsored by individual investigators, academic institutions, and non-profit entities
  - Can be clinical investigation or clinical treatment (expanded access)
  - May be converted to commercial as development progresses

21 CFR 312.320, 312.310, 312.315, and 312.320

Research INDs

- Typically for academic investigators, a clinical investigation with an unapproved drug
- May also involve “expanded access” for patients with serious or immediately life-threatening diseases without alternative treatment options if the potential patient benefit justifies the potential risks of the treatment and the potential risks are not unreasonable

https://www.fda.gov/drugs/investigational-new-drug-ind-application/ind-applications-clinical-treatment-expanded-access-overview
https://www.fda.gov/drugs/types-applications/investigational-new-drug-ind-application

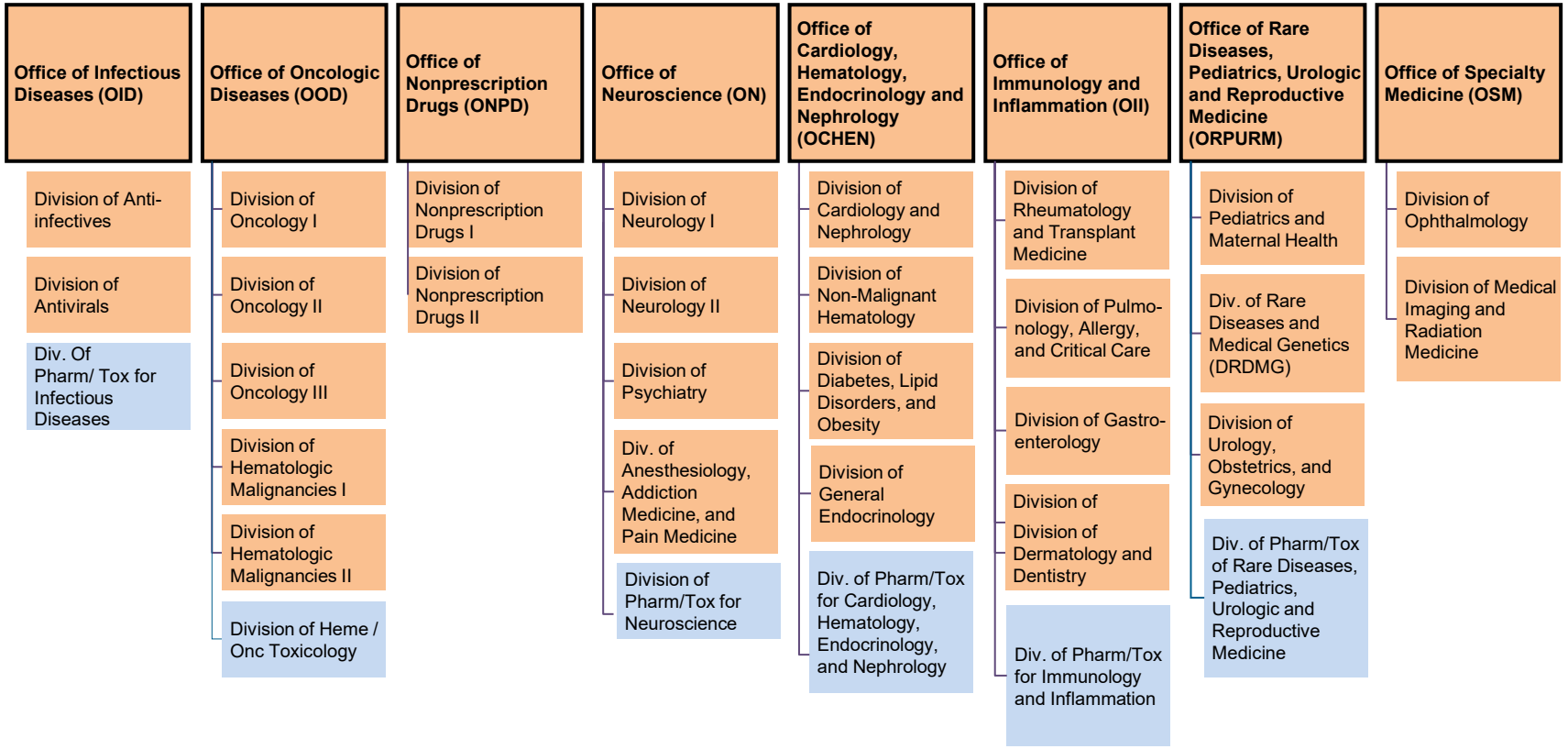
Pre-IND consultation

Discussion with therapeutic area division:

- Data requirements for IND application
- Data needed to support rationale for testing drug in humans
- Design of animal model studies (nonclinical pharmacology, toxicology) and drug activity studies
- Initial drug development plans
- Regulatory requirements for safety and efficacy demonstration

21 CFR 312.82

CDER's Office of New Drugs



https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/cder-offices-and-divisions

Pre-IND interaction tips

- Provide context for the IND (past use of drug)
- Pose specific and direct questions to FDA, which may be answered in writing
- Provide relevant brief summaries of animal or human studies data on the drug and discuss the scope and design of your first in human study

Formal Meetings between FDA and Sponsors

- Submit a meeting request
- Sponsor seeks advice and concurrence
- FDA will grant (and determine the meeting format) or deny the meeting.
- Follow the Guidance at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/formal-meetings-between-fda-and-sponsors-or-applicants-pdufa-products-guidance-industry

IND Application Content (1)

Requirements outlined in **21 CFR 312.23**

- Cover Letter
- Form FDA 1571
- Form FDA 3674
- Table of Contents
- Introductory Statement/General Investigational Plan
- Investigator's Brochure (required for multiple investigators; single investigators do not need)

https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-312?toc=1

Content (2)

- **Nonclinical**
  - Animal pharmacology and toxicology studies
  - Sufficient pre-clinical data to support clinical protocol
  - Basic exposure data

Reference: International Council for Harmonization (ICH) guidelines
https://www.ich.org/page/ich-guidelines

Content (3)

- **Chemistry, manufacturing, and controls**
  - Sufficient information to assure proper identification, quality, purity, and strength
  - Sufficient information to assess whether batches can be adequately produced and consistently supplied

Content (4)

- **Clinical protocol**
  - Determine the phase of development
  - Provide supporting data (e.g., from foreign/ex-U.S. trials, PK data)
  - Specify how to ensure safety of the subjects/patients in the study (common reason INDs are placed on clinical hold)
  - Provide investigational drug dose titration plans, laboratory or imaging study plans, clinical visit assessment plans

Content (5)

- Clinical investigator qualifications (curriculum vitae, disclosure of financial interests in FDA 1571 or 3674)
- Informed consent for research subjects
- IRB review plans

21 CFR 312.88

IND Application: Sending it in

- Electronically in Common Technical Document (eCTD) format (research or commercial)
- Electronically through the NextGen portal on the Internet (research only)
- Electronically through the Reagan-Udall Foundation on the internet (expanded access INDs only)
- Mail to the document room (research only)

  Food and Drug Administration
  Center for Drug Evaluation and Research
  Division of XXXXX
  5901-B Ammendale Road
  Beltsville, MD 20705-1266

https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/requesting-pre-assigned-application-number

After IND Submission: Initial Steps

- Review team assembled:
  - Clinical
  - Regulatory
  - Nonclinical pharmacology/toxicology
  - Chemistry
  - Clinical pharmacology
  - Biostatistics (if phase 3 protocol)
  - Consult reviewers as needed (ex. device, botanical, ethics)

The First 30 Days

- Safety Review
  - The review division will determine within **30 days** of receipt of the IND whether the study is “reasonably safe to proceed” (active) or will be placed on clinical hold
  - INDs are not approved
- If FDA determines that an IND meets exemption criteria, it will be exempted

Safety Review

Includes many aspects, including:

- Safety monitoring in treatment protocol
  - Type and frequency of laboratory testing, ECGs, clinical monitoring
  - Monitoring for known safety signals with drug
  - Criteria for drug dose titration or discontinuation
  - Drug stopping criteria, including parameters for lack of efficacy
- Product information
  - Drug dosage and formulation
  - Route of administration and frequency

Interactions within 30 days

- FDA information requests (IR) will be communicated to the Sponsor or authorized representative only
- IR responses/IND application revisions should be submitted through established methods, e.g. NextGen Portal
- After 30 days, unless placed on clinical hold, an investigation drug may be administered
- A drug manufacturer may ship the investigation drug to the investigator(s) once an IND is in effect

Clinical Hold

An order issued by FDA to the sponsor of an IND to delay a proposed clinical investigation or suspend an ongoing clinical investigation

- Full Clinical Hold: all clinical studies under an IND
- Partial Clinical Hold: only part/some of clinical studies under an IND (e.g., a specific protocol or part of a protocol is allowed to proceed)

21 CFR 312.42(a)

Clinical Hold (continued)

- Grounds for clinical hold for Phase 1 trials:
  - Human subjects would be exposed to an unreasonable and significant risk of illness or injury;
  - clinical investigators are not qualified;
  - investigator brochure is misleading, erroneous, or materially incomplete;
  - insufficient information to assess risks to subjects;
  - exclusion by gender for life-threatening disease or condition (unless justified/special circumstances)

21 CFR 312.42(b)(1)

Clinical Hold (continued)

- Grounds for clinical hold for Phase 2/3 studies:
  - Any reason listed above for Phase 1 trials;
  - the protocol is deficient in design to meet its stated objectives

21 CFR 312.42(b)(2)

Clinical Hold (continued)

- If a deficiency is identified that may be grounds for imposing a clinical hold:
  - The review division may send an IR and/or request changes to the proposed protocol
  - Potential holds may be resolved through such communication (e.g., inadequate patient monitoring)
  - If unresolved, a letter is sent

Clinical Hold (continued)

- A response to the clinical hold letter:
  - Should be complete (i.e., address all the deficiencies identified in the letter) otherwise the response will be deemed incomplete, a letter will be sent, and the response will not be reviewed
- Review division will respond within **30 days** of receipt of the response by either:
  - Removing the clinical hold;
  - Continuing the clinical hold;
  - Modifying the clinical hold (e.g., full to partial or partial to full)

Sponsor Responsibilities

- Record keeping and record retention
  - Receipt, shipment, and disposition of the investigational drug
  - Financial interest paid to investigators
  - Retain records for two years after drug approved OR investigations are discontinued
  - Retain reserve samples of any test article and reference standard identified in, and used in any of the bioequivalence or bioavailability studies

21 CFR 312.57

Sponsor Responsibilities

- Permit FDA inspection of records and reports
  - Provide copies of records and reports upon written request
- Disposition of unused drug or assure return of all unused supplies of the investigational drug
  - Ensure safe disposition (does not expose humans to risks)

21 CFR 312.58, 21 CFR 312.59

Investigator Responsibilities

- Ensure that the investigation is conducted according to the protocol and applicable regulations, protect the rights, safety, and welfare of subjects (including informed consent)
- Control of the investigational drug
  - Administer drug only to subjects
  - Do not supply the drug to anyone not authorized to receive it

21 CFR 312.60, 21 CFR 312.61

Investigator Responsibilities

Recordkeeping and record retention

- Case histories [e.g., Case Report Forms (CRFs) and supporting data, signed and dated consent forms, medical records]
- Disposition of the investigational drug (dates, quantity, and use by subjects)
- Retain records for 2 years after drug is approved for the indication being investigated or 2 years after the investigation is discontinued

21 CFR 312.62

Investigator Responsibilities

- **Investigator reports to the sponsor**
  - Progress reports
  - Safety reports
  - Final report
  - Financial disclosure reports
- Permitting FDA inspection of records and reports
- Handling of controlled substances
  - Securely locked; limited access

Investigator Responsibilities

- **Assurance of IRB review**
  - Assure that an IRB is responsible for review and approval of the protocol
  - Report any unanticipated problems involving risk to subjects
  - Not make any protocol changes without IRB approval except to eliminate immediate hazards to subjects

21 CFR 312.68, 21 CFR 312.69

IND Amendments

- Protocol amendments
  - New Protocol
  - Changes in Protocol
  - New Investigator

- Information amendments

21 CFR 312.30, 21 CFR 312.31

New Protocol

- New study may begin provided:
  - Submitted to IND
  - Approved by IRB

Changes in Protocol (1)

- Protocol changes may be implemented provided:
  - Change submitted to IND
  - Approved by IRB

  Exception: Change to eliminate an apparent immediate hazard to subjects can be implemented immediately.

21 CFR 312.30(a)

Changes in Protocol (2)

- Submit
  - Copy of the protocol, identifying significant differences from previous protocols (i.e., tracked changes version)
  - Request for comment (optional)

Information Amendments

- Amendment required for submission of essential information not within scope of protocol amendment, safety report, annual report
  - New information (e.g., clinical, clinical pharmacology, nonclinical, chemistry, study reports)
  - Discontinuance of study (within 5 days of decision)

21 CFR 312.31

IND Reporting Requirements

- Safety Reports
- Annual Reports

21 CFR 312.32, 21 CFR 312.33

Safety Reports: Definitions (1)

- Serious: An adverse event (AE)/serious adverse reaction (SAR) that, in the view of the investigator or sponsor, results in:
  - death
  - life-threatening AE
  - in-patient hospitalization/prolonged hospitalization
  - a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
  - congenital anomaly/birth defect
  - medical/surgical intervention to prevent one of these outcomes

21 CFR 312.32(a)

Safety Reports: Definitions (2)

- Unexpected: An AE/SAR that is not listed in the Investigator Brochure (IB) or not listed at the specificity/severity observed; or if no IB, inconsistent with the risk information described in the general investigational plan.

Annual Report (1)

Report of the progress of the investigation that includes:

- Individual study information
  - Title, purpose, patient population, study status
  - Total number (#) of subjects planned, # entered to date, by age group, gender, and race; the # completed as planned, # drop-outs
  - Study results, if completed

21 CFR 312.33

Annual Report (2)

Summary Information:

- Most frequent and most serious AEs
- Summary of all IND safety reports submitted during past year
- Study drop-outs due to AEs
- Include list of subjects who died
- Completed and in-progress nonclinical studies during the past year, and summary of major findings
- CMC changes
- General investigational plan for coming year
- Revisions to the Investigator Brochure

Other Activities

- Inactivation

  Sponsor or FDA may initiate inactivation if:

  - No subjects enrolled into studies for ≥2 years
  - All investigations on clinical hold for ≥1 year
- Reactivation
  - Sponsor submits a protocol amendment
  - 30 day waiting period
- Withdrawal
- Termination

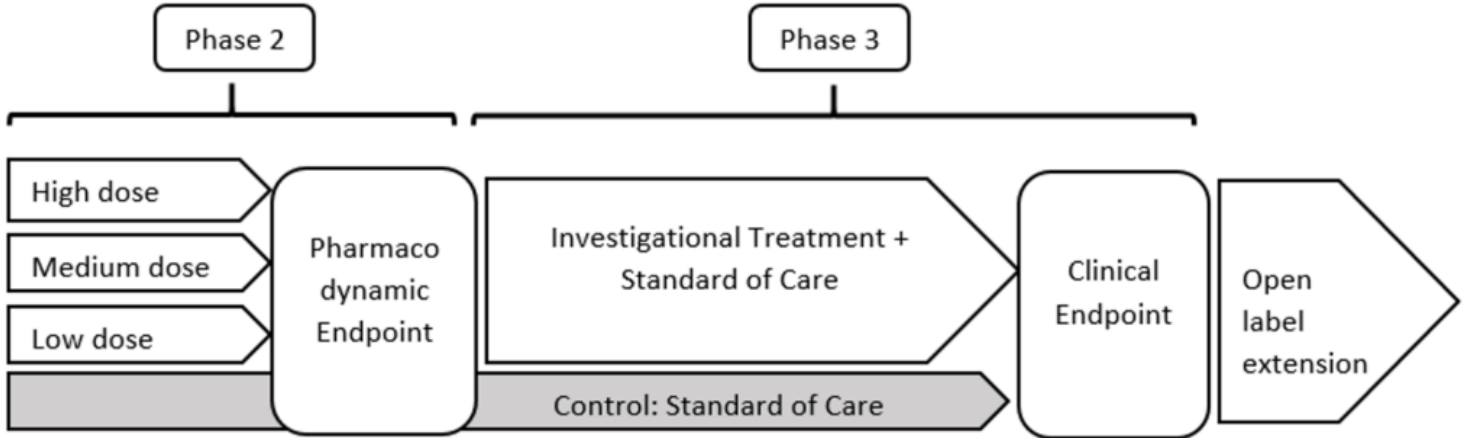
21 CFR 312.45, 21 CFR 312.45(d), 21 CFR 312.38, 21 CFR 312.44

And Don’t Forget…

- Adequate safety monitoring
  - Laboratory studies, ECGs
- Drug dose titration plan, administration plans with food, and treatment duration
- Include drug stopping criteria
  - life-threatening adverse events/reactions, serious adverse events
  - the patient discontinues (if a single patient)

INDs with intent to develop a new clinical indication

For a well-controlled study, when there are few patients, consider the best drug trial design to optimize chance of demonstrating drug efficacy and safety (e.g., instead of a phase 1 trial only, plan for an adaptive trial design to roll over patients into a seamless phase 2/3 trial)



FDA Guidance: Adaptive Designs for Clinical Trials of Drugs and Biologics
https://www.fda.gov/media/78495/download

INDs with intent to develop a new clinical indication

- Phase 1 study may assess pharmacokinetics and safety
- For Phase 2/3 trial, endpoint(s) and duration should reflect clinically meaningful change, defined as how a patient feels, functions, or survives
- Adequate trial duration to show clinically meaningful change, especially in slowly progressive diseases
- Bioanalytical assays may need further data on reproducibility and FDA validation with CDRH (e.g. companion diagnostics)

Reference: In Vitro Companion Diagnostic Devices
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/in-vitro-companion-diagnostic-devices

Informed consent tips

- Appropriate consent for any genetic testing
  - Specific genes that will be sequenced
  - Clause on genetic study exclusion, such as “No other information about your DNA will be determined”
- Patient privacy expectations
  - Your records will be kept as private as possible under law
  - Encoding of personal identification

Take-away points

- Consider what type of IND your investigation fits: https://www.fda.gov/drugs/types-applications/investigational-new-drug-ind-application

- Follow the guidance for requesting formal meetings with FDA: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/formal-meetings-between-fda-and-sponsors-or-applicants-pdufa-products-guidance-industry

- Remember investigator responsibilities for IND

FDA Resources

- IND forms and instructions https://www.fda.gov/drugs/investigational-new-drug-ind-application/ind-forms-and-instructions

- CDER's Office of New Drug Divisions
  https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/cder-offices-and-divisions

Pediatric Considerations in Rare Disease Drug Development

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Office of New Drugs (OND), CDER, FDA

Outline

- Background: Pediatric Drug Development

- Regulatory Challenges and Opportunities
  - Requirements under the Pediatric Research Equity Act (PREA)
  - Incentives under Best Pharmaceuticals for Children Act (BPCA)
  - Orphan Drug Designation

- Unique Pediatric Considerations and Challenges
  - Regulatory
  - Ethics
  - Study Design

- Strategies to overcome challenges in conducting trials in rare pediatric diseases.

Acronyms

- BPCA Best Pharmaceuticals for Children Act
- FD&C Act Food, Drug, and Cosmetic Act
- FDAMA Food and Drug Administration Modernization Act
- FDASIA Food and Drug Administration Safety and Innovation Act
- PREA Pediatric Research Equity Act
- WR Written Request

Pediatric Drug Development: Past

- Reluctance to study drugs in pediatric patients
  - Ethical concerns
  - Financial constraints
  - Trial design challenges

- Lack of incentives or requirements for the conduct of pediatric trials

Pediatric Drug Development: Past

More than 80% of approved drugs had no pediatric-specific information

Dilemma for Pediatric Prescribers

- Not treat pediatric patients with potentially beneficial drugs because they were not approved or studied for pediatric use

- Use off-label based on adult trials and limited, if any, pediatric anecdotal experience

Pediatric Drug Development: Present

General Principles

- Evolved from view that we must protect pediatric patients from research to a view that we must protect them through research

- Include pediatric patients in drug development programs when pediatric use is anticipated

- Discourage off-label use

E11(R1) Addendum: Clinical Investigation of Medicinal Products in the Pediatric Population (April 2018)

The Pediatric Research Equity Act

- Requires companies to assess safety and effectiveness for drug products that are submitted for marketing approval for new active ingredients, new indication(s), new dosage forms, new dosing regimens, or new routes of administration.
  - An assessment is required to support more effective labeling in all relevant pediatric age groups for the same indication(s) being sought in adults – unless the requirement is waived or deferred

- Requires the development of an age-appropriate formulation to conduct required studies but does not require companies to market the formulation.

- Does not currently apply to products granted Orphan Designation.
  - Exception: drugs/biologics being developed for adult cancer with molecular targets relevant to growth/progression of pediatric cancer*

* 505B(a)(1) of the FD&C Act (8/18/2020)

Best Pharmaceuticals for Children Act

- The 1997 Food and Drug Administration Modernization Act (FDAMA) first allowed FDA to issue a Written Request (WR).

- BPCA provides financial incentives to companies that voluntarily conduct FDA-requested pediatric studies of an active moiety for indications which could provide health benefit (e.g. through a WR).

- WR should include studies of all potential pediatric indications for which the active moiety in the drug product could provide use and benefit.

- The financial incentives are an additional 6 months of marketing exclusivity to a sponsor who completes the studies outlined in the WR.

Ultimate Goal of PREA and BPCA

⬇

New Pediatric Labeling

to inform appropriate use of drugs and biologics to treat pediatric patients

Rare Disease Incentives: Orphan Drug Designation

- Orphan Drug Act of 1983 promotes development and evaluation of new treatments for rare diseases and provides sponsors/companies with:
  - Tax credits for up to half of qualified clinical trial costs
  - Waiver of the Prescription Drug User Fee Act filing fee
  - Potential for seven years of market exclusivity after approval

- A "rare disease or condition" is defined as affecting less than 200,000 persons in the U.S. or affects more than 200,000 persons in the U.S. and for which there is no reasonable expectation that the cost of developing and making available in the U.S. a drug for such disease or condition will be recovered from sales of such drug.

Unique Rare Pediatric Disease Considerations and Challenges

- Regulatory
- Ethics
- Study Design
  - Limitation on the understanding of the natural history of disease
  - Extrapolation
  - Lack of precedent for drug development in the disease/condition

Rare Pediatric Disease Incentives: Rare Pediatric Disease Priority Review Voucher Program

- A Sponsor who receives marketing approval for a drug or biologic for a “rare pediatric disease” may qualify for a voucher that can be redeemed to receive a priority (i.e. 6 month) review of a subsequent marketing application for a different product.
- Revised draft guidance posted July 2019
- Rare Pediatric Disease defined as:
  - A serious or life-threatening disease in which the serious or life-threatening manifestations primarily affect individuals age birth to 18 years and the disease is a rare disease as defined in section 526 of the FD&C Act.
- Sunsets on September 30, 2024

Added as section 529 of the FD&C Act by FDASIA

Ethical Considerations in Pediatrics

- Can scientific and/or public health objective(s) be met by enrolling subjects who can provide informed consent personally (i.e., adults)?
  - Subjects capable of informed consent (i.e., adults) should be enrolled prior to children (21 CFR 56.111(a)(1) and (b)])
  - Do not enroll children unless essential (i.e., no other option, whether animal or adult human)

- Does trial participation offer prospect of direct benefit?
  - If not, then risks to which a child would be exposed in a clinical trial must be “low” (21 CFR 50.51 and 50.53)
  - Obtaining generalizable knowledge to be able to treat others not considered a direct benefit to a pediatric patient

Pediatric-Specific Diseases: Natural History of Disease

- Knowledge of natural history of a rare pediatric disease is **critical** to successful drug development.

- Key considerations for natural history studies:
  - Define disease population and identify key disease subtypes
  - Inform clinical trial design (e.g. entry criteria, study duration)
  - Inform selection of primary outcome measure(s) - Biomarkers
  - Potentially provide external control group

- Make these data publicly available to promote drug development.

Rare Pediatric Disease: Natural History Study Design

- Broad inclusion criteria with a wide spectrum of phenotypes and severity
- Sufficient duration to capture clinically meaningful outcomes and variability
- Identify when specific manifestations develop and are likely to persist
- Standardized methods to collect relevant clinical data

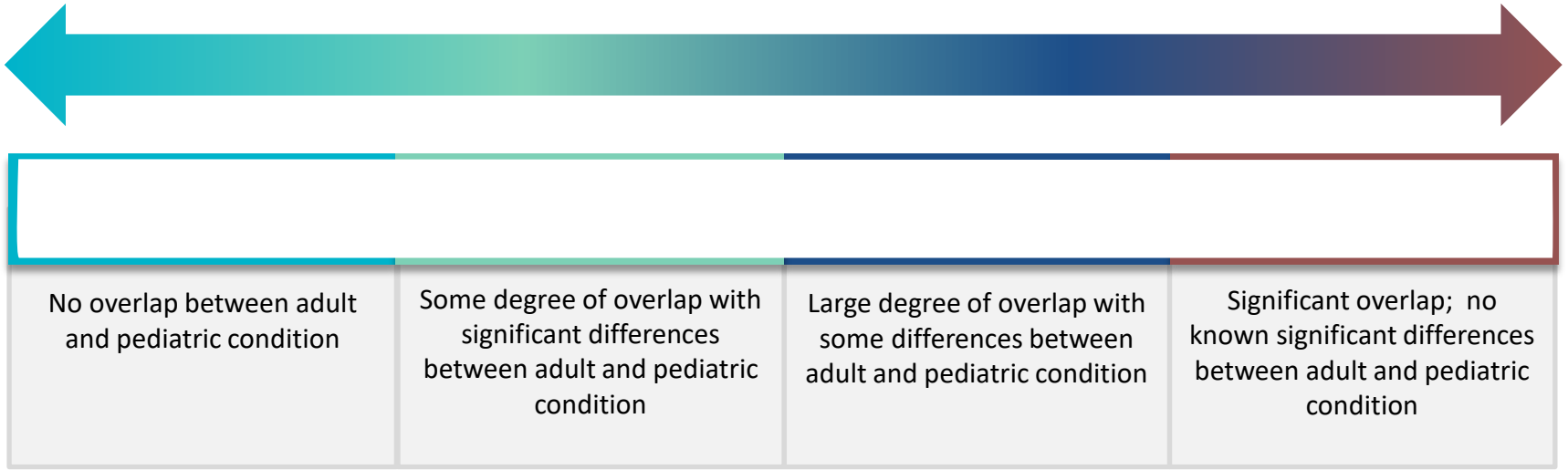
Trial Design Strategies

- Pediatric extrapolation from a reference population
  - Improves efficiency and reduces sample size
  - Relies on key assumptions that the extrapolated pediatric population has a similar disease course and expected response to therapy as the reference population
- Joint adult-pediatric trials
  - Include pediatric population based on disease biology rather than simply chronological age
- Conduct separate pediatric trial(s) in parallel with adult phase 3 trial(s)
  - Consider bridging biomarkers, Bayesian approaches

Momper JD, Mulugeta Y, Green DJ et al. Adolescent Dosing and Labeling Since the Food and Drug Administration Amendments Act of 2007. JAMA Pediatrics 167 (10): 926-932, 2013

Extrapolation of Efficacy

Disease/Response "Similarity" is a Continuum



Trial Design Strategies

- Use of non-concurrent (e.g. historical) controls
- Innovative trial designs
  - Make efficient use of a limited patient population for enrollment (e.g. Seamless trial design)
  - Innovative approaches (e.g. interim analyses)
- Multiple endpoint strategies
  - Carefully consider the use of biomarkers and intermediate clinical endpoints as surrogate endpoints

Momper JD, Mulugeta Y, Green DJ et al. Adolescent Dosing and Labeling Since the Food and Drug Administration Amendments Act of 2007. JAMA Pediatrics 167 (10): 926-932, 2013

Collaboration

- Trials are often global by necessity to recruit sufficient patients for rare pediatric diseases.

- Collaboration between the FDA and international regulatory agencies facilitates harmonization of trial designs.
  - The Pediatric Cluster: Common Commentary
  - The Rare Disease Cluster
  - Parallel Scientific Advice

Conclusions

- The development of drug products to treat rare pediatric diseases and conditions is vitally important.
- Regulatory, ethical, and trial design considerations represent unique challenges and opportunities in pediatric rare disease drug development.
- Strategies to facilitate the successful completion of trials that yield interpretable efficacy and safety data continue to evolve.

Resources

FDA Report to Congress on BPCA and PREA

Rare Pediatric Disease Priority Review Voucher Program

Rare Diseases: Natural History Studies for Drug Development Draft Guidance

Rare Diseases: Common Issues in Drug Development Draft Guidance

Pediatric Rare Diseases - A Collaborative Approach for Drug Development; Draft Guidance

Thank You

Nonclinical Perspective on the Development of Drugs for Rare Diseases

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CDER/FDA

Outline

- Objective of nonclinical studies
- Types of nonclinical studies to support drug development
- Things to consider during drug development
- Timing for conducting nonclinical studies
- Issues specific for rare diseases

Objective of the Nonclinical Studies

SAFETY

- Assess the safety profile of a pharmacological product based on the available in vitro and in vivo data
- Predict how exposure and toxicity in animal models will correlate in humans

Types of Nonclinical Studies

- Pharmacology
  - Primary and secondary pharmacodynamics
  - Safety pharmacology (ICH-S7A)
- Pharmacokinetics/Toxicokinetics
  - Absorption, Distribution, Metabolism, Excretion (ADME)
- Toxicology
  - Single-dose toxicity
  - Repeat-dose toxicity (ICH M3R(R2))
  - Genotoxicity (ICH-S2(R1))
  - Carcinogenicity (ICH-S1A, ICH-S1C(R2))
  - Reproductive and developmental toxicity (ICH-S5(R3))
  - Local tolerance
  - Phototoxicity (ICH-S10)
  - Immunotoxicity (ICH-S8)
  - Abuse potential

Pharmacodynamics

- Pharmacodynamics – the study of the physiological effects of a drug (what the drug does to the body)
- Preliminary studies that demonstrate proof of concept and mechanism of action
  - *In vitro* studies – receptor binding, functional activity
  - *In vivo* studies – nonclinical efficacy studies
- Do not need to show definitive efficacy to proceed; studies are conducted more for candidate election/prioritization
- Understanding how the pharmacology impacts interpretation of toxicology studies

Safety Pharmacology

- Studies that identify potential adverse pharmacodynamic effects of a drug on normal physiological functions

- Core Battery
  - Cardiovascular (hemodynamics, ECG)
  - Respiratory (spirometry, airway resistance/lung compliance)
  - Central nervous system (functional observational battery)

Pharmacokinetics

- Pharmacokinetics – the study of what the body does to the drug
- Studies that assess how a drug is absorbed, distributed, metabolized and excreted from the body (ADME)
- Generally conducted as single-dose studies in animals at non-toxicological dose levels
  - May use a radioactive form
  - Supports nonclinical toxicology study doses
  - Help predict human PK parameters
- Toxicokinetics – pharmacokinetics in animal models at doses used in the toxicology studies
  - Usually integrated into the repeat-dose toxicology studies
  - Data used to correlate drug exposure to toxic endpoints

Repeat-Dose Toxicology Studies

- Studies that determine the adverse effects of a drug in animals
  - Needed to support initiation of clinical trials
  - Longer clinical protocols require longer repeat-dose studies
- Pivotal in determining whether the proposed clinical trial is safe to proceed
  - Identify toxicities of concern
  - Determine what clinical monitoring will be needed
  - Define a No Observed Adverse Effect Level (NOAEL) and calculate safety margins

Recommended Duration of Studies

Table 1 Recommended Duration of Repeated-Dose Toxicity Studies to Support the Conduct of Clinical Trials

Maximum Duration of Clinical Trial	Recommended Minimum Duration of Repeated-Dose Toxicity Studies to Support Clinical Trials	
	Rodents	**Nonrodents**
Up to 2 weeks	2 weeks[a]	2 weeks[a]
Between 2 weeks and 6 months	Same as clinical trial[b]	Same as clinical trial[b]
> 6 months	6 months[b, c]	9 months [b, c, d]

Table 2 Recommended Duration of Repeated-Dose Toxicity Studies to Support Marketing

Duration of Indicated Treatment	Rodent	Nonrodent
Up to 2 weeks	1 month	1 month
>2 weeks to 1 month	3 months	3 months
>1 month to 3 months	6 months	6 months
>3 months	6 months[c]	9 months [c, d]

Repeat-Dose Toxicology Studies

- Key parameters to be evaluated:
  - Mortality and clinical signs
  - Body weight and food consumption
  - Clinical pathology
    - Hematology
    - Clinical chemistry
    - Clotting parameters
    - Urinalysis
  - Ophthalmology
  - Pathology
    - Gross pathology
    - Organ weights
    - Histopathology
  - Local tolerance
  - Toxicokinetics
- Nonclinical safety review considerations:
  - Were the studies conducted according to GLP requirements?
  - Are the toxicities sex- or species-specific?
  - Are the toxicities dose-dependent? Are they reversible?
  - What are the expected clinical toxicities? Are they monitorable?
  - Is there a well-defined NOAEL? Is the proposed trial safe to proceed?
  - Are additional studies needed?

Genotoxicology and Carcinogenicity

- Genotoxicology: Studies that assess the ability of a drug to induce genetic damage
  - Short-term *in vitro* and *in vivo* studies
  - Used to identify mutagens and clastogens

- Carcinogenicity: Studies that assess the carcinogenic potential of a drug
  - Long-term *in vivo* studies
  - Required, generally prior to approval, for drugs intended to be administered for at least 6 months per year (continuous or intermittent)

Reproductive Toxicology

- Studies that evaluate the ability of a drug to adversely effect fertility, pregnancy and embryo-fetal/neonatal development

- Types of reproductive and developmental toxicology studies
  1. Fertility and early embryonic development study
  2. Embryo-fetal development (EFD) study
  3. Prenatal and postnatal development (PPND) study

Special Toxicology Studies

- Performed when there is a specific cause for concern based on:
  - Mechanism of action
  - Drug class
  - Signal identified in toxicology studies

- Endpoints are limited to those necessary to address the specific concern

- Examples:
  - Phototoxicity
  - T-Dependent Antigen Response (TDAR)
  - Mitochondrial Toxicity

Important Clinical Considerations

- Do the nonclinical findings support the proposed clinical protocol(s)?
  - Starting dose and dose escalation
  - Duration and frequency of dosing
  - Route of administration
  - Patient population
- Is there previous clinical experience?
- Can the toxicities be monitored in humans; will special monitoring be needed?

Important Clinical Pharmacology Considerations

- How do animal and human PK/TK data compare?
  - Are there relevant comparisons?
  - Is a specific model a more relevant species?
  - How do maximum human exposures correlate to exposures in animals?
- How does exposure relate to toxicity?
  - C_{max} (peak drug concentration) vs. AUC (total amount of drug circulating in the body)
- If there are multiple human studies, what PK/TK data are most appropriate for determining safety?

Important Chemistry Considerations

- Are there structural alerts or reactive groups of concern?
- Is the formulation appropriate?
  - Excipients
  - Impurities
  - Leachables
- Are there differences in the clinical and nonclinical drug substance profiles?

Studies Needed Prior to First-in-Human Exposure

- Pharmacodynamics/Pharmacokinetics
- Safety pharmacology core battery
- General toxicology studies (single/repeat dose, rodent and non-rodent, study design dictated by proposed clinical trial)
- Genetic toxicity (*in vitro* studies for mutagenesis and clastogenesis)
- Local tolerance (dependent on the route of administration)

As Clinical Trials Proceed

- Longer-duration toxicity studies may be needed to cover longer clinical trials or to support marketing approval
- Genetic toxicology studies should be completed
- As data are collected, animal and human exposure comparisons can be made
- Reproductive toxicity testing (fertility and EFD before Phase 3, PPND for marketing approval)
- Carcinogenicity and other studies may be recommended

Special Considerations for Rare Diseases #1

- FDA may apply additional flexibility in evaluating development programs for drugs to treat serious and life-threatening diseases
  - Rare Disease: Common Issues in Drug Development (draft, 2019)
  - Investigational Enzyme Replacement Therapy Products: Nonclinical Assessment (final, 2019)

- Timing and specific design of nonclinical studies can vary with the type of drug or biological product being studied
  - Some toxicology studies deferred to post-marketing (e.g., reproductive developmental toxicology studies)

- Agreement needed with the FDA for flexibility in nonclinical program
  - Seek feedback early with FDA (i.e., during pre-IND meetings)
  - Written justification should be provided
  - Flexible nonclinical program requests are assessed on a case-by-case basis; largely driven by patient population

Special Considerations for Rare Diseases #2

- Nonclinical pharmacology studies may inform potential clinical benefit of a drug on disease pathophysiology
  - Example - lack of extensive natural history of disease
  - May show prospect of direct benefit
- Animal models should resemble clinical disease phenotype
- Proof of concept assessment of drug treatment in relation to patients to show how patient may survive/function
  - Animal survival
  - Functional improvement
  - Biochemical improvement

Special Considerations for Rare Disease #3

- Compelling mechanistic evidence from pharmacology studies may support confirmatory evidence for marketing applications
  - Agreement needed with the FDA
  - Seek feedback early with FDA (i.e., during pre-IND meetings)
  - Written justification should be provided

Case Study: Weight of Evidence (WOE) Approach for Carcinogenicity Studies

- Avalgulcosidase alfa-ngpt (BLA 761194)
  - Enzyme replacement therapy (ERT) for Pompe disease (glycogen storage disease type II late onset)
  - 20 mg/kg IV Q2W for patients ≥30 kg and 40 mg/kg IV Q2W for patients ≤30 kg
  - Approved in 2021

Case Study: Weight of Evidence (WOE) Approach for Carcinogenicity Studies

- ICH S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals
  - Genotoxicity studies are not applicable and are therefore not needed
  - Standard carcinogenicity bioassays are generally inappropriate but may be needed depending on the duration of use, patient population and/or biological activity of the product

- Enzyme Replacement Therapy guidance (October 2019)
  - Carcinogenicity studies are generally not needed for marketing unless they are conjugated with a chemical linker then an assessment may be warranted

Case Study: Weight of Evidence (WOE) Approach for Carcinogenicity Studies

- Non-GLP in vivo micronucleus test was conducted in GAAKO mice with up to 150 mg/kg IV – negative for genotoxicity

- Applicant submitted a carcinogenicity risk assessment including:
  1. Evaluation of the nonclinical toxicity
     - No histopathology findings in the 26-week repeat-dose toxicity study in monkeys
  2. Review of marketed Pompe disease drugs
  3. Review of impurities based on published literature, a 13-week repeat-dose toxicity study with the impurity in monkeys, and in vitro genotoxicity studies (Ames and chromosomal aberration assays)
     - Lack of toxicity in monkeys and negative for genotoxicity
  4. Evaluation for the potential release of impurities from the drug product

- FDA's conclusion: A postmarketing carcinogenicity study was not warranted based on a weight of evidence

Nonclinical Guidances

ICH guidance list:	http://www.ich.org/products/guidelines.html
FDA guidance list:	http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm
ICH-M3(R2):	Nonclinical safety studies for the conduct of human clinical trials for pharmaceuticals
ICH-M7:	Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk
ICH-S1B:	Testing for carcinogenicity of pharmaceuticals
ICH-S1C(R2):	Dose selection for carcinogenicity studies of pharmaceuticals
ICH-S2(R1):	Genotoxicity testing and data interpretation for pharmaceuticals intended for human use
ICH-S5A:	Detection of toxicity to reproduction for medicinal products
ICH-S6(R1):	Preclinical safety evaluation of biotechnology-derived pharmaceuticals
ICH-S7A:	Safety pharmacology studies for human pharmaceuticals
ICH-S7B:	Nonclinical evaluation of the potential for delayed ventricular repolarization (QT interval prolongation) by human pharmaceuticals
ICH-S8:	Immunotoxicity studies for human pharmaceuticals
FDA Guidance for Industry:	Estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers


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SESSION 5: THE NUTS AND BOLTS OF INVESTIGATIONAL NEW DRUG (IND) APPLICATIONS AND ADDITIONAL CONSIDERATIONS

Moderator: Cynthia Welsh, M.D., Medical Officer, RDT, DRDMG, ORPURM, OND, CDER, FDA

We'll be back after this short break...

SESSION 6: ADDITIONAL PATHWAYS TO INTERACT WITH FDA CDER

FDA U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION & RESEARCH

ADDITIONAL PATHWAYS TO INTERACT WITH FDA/CDER

Critical Path Innovation Meetings

Patient Focused Drug Development

Critical Path Innovation Meetings (CPIM)

CDR Chekesha Clingman-Henry
Associate Director for Strategic Partnerships
Office of Translational Sciences, CDER, FDA

Background

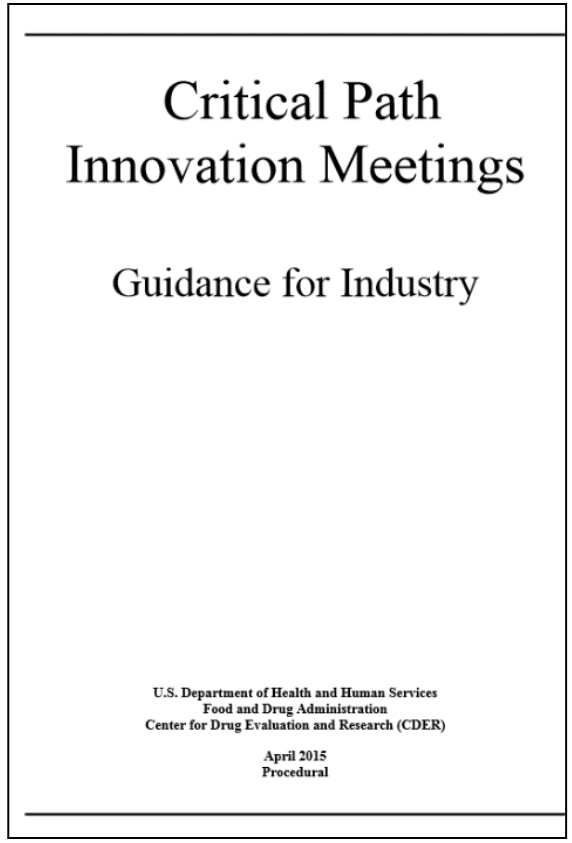
The 2004 FDA publication, *Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products Challenges and Opportunities Report* identified several areas of product development in need of improvement and cited a need “to create better tools for developing medical technologies [and] a knowledge base built not just on ideas from biomedical research, but on reliable insights into the pathway to patients.”

Goal of the CPIM

Critical Path Innovation Meeting (CPIM) provides an opportunity for stakeholders to communicate directly with FDA subject matter experts and have an open scientific discussion and exchange of ideas with a common goal of improving efficiency and success in drug development

Critical Path Innovation Meeting (CPIM)

- Discussion of the science, medicine, and regulatory aspects of innovations in drug development; nonbinding
- Not a meeting about a specific approval pathway
- Scope includes early biomarkers and clinical outcome assessments, natural history studies, technologies (not manufacturing), and clinical trial designs and methods
- CDER provides perspective on role of innovation in drug development and potential future research efforts



https://www.fda.gov/media/89497/download

CPIM Logistics

- Anyone with a role in drug development can request a CPIM.
- Requester fills out a one page form on the website.

- CPIM staff will evaluate the form to identify if CPIM is the right venue for the discussion.
- Acceptance of a CPIM is based on the relevance of the topic to drug development.
- CPIM staff work to identify subject matter experts and request their participation for the CPIM. In some cases, subject matter experts are invited from other Centers, including the Center for Biologics Evaluation and Research and the Center for Devices and Radiological Health.

CPIM Logistics

- Requester provides slides two weeks before the CPIM
- Pre-CPIM meeting one week before the CPIM
  - Orient internal participants to meeting structure
  - Identify areas to discuss/not discuss
  - Identify other participants to be invited

- 1.5 hours in length
- Presentation/scientific discussion led by the requester
- No discussion of policy, guidance, individual drug development programs
- Last 5-10 minutes for next steps

CPIM Topics

- Clinical Trial Endpoints
- Biomarker Development
- Drug Development Tools
- Innovative Trial Designs
- Clinical Trial Networks
- Natural History Studies
- COA Development
- Rare Diseases
- Databases
- Registries

CPIM Outcomes

- Brief, high-level summary written by CPIM Program and shared with the requester
- Topic area added to the website
- Outcomes have included: follow up with a specific CDER office/division/program or another Center; suggestion to have a public workshop or collaborate with other external groups; RCA/CRADA
- 102 meetings held since the program's launch in 2013; approximately 30% on rare disease drug development

Tips for a Successful CPIM

- **Expectations:**
  - High-level discussion of science, technology, innovative strategies to advance drug development
  - Two-way exchange of ideas between FDA and requester
  - No discussion of policy, specific development pathway, or detailed review of data
- **Meeting Request:**
  - Clear, brief description of the meeting purpose, background, steps taken to advance the project, specific questions for FDA, and desired outcomes
- **Meeting Package Submission:**
  - Objectives, presentation, agenda
  - Prioritize questions and feedback
  - 2 weeks in advance
- **Meeting Day:**
  - Requester leads the discussion (only 90 mins-manage your time)
  - Ask clarifying questions
  - Leave 10 mins to recap/discuss next steps

For more information

CPIM Website:

https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/critical-path-innovation-meetings-cpim

If you have questions, please send inquiries to:

CPIMInquiries@fda.hhs.gov

Patient-Focused Drug Development

Robyn Bent, RN, MS | CAPT, U.S. Public Health Service

Director, CDER PFDD Program

Office of the Center Director

Center for Drug Evaluation and Research (CDER)

Patients in Drug Development and Regulatory Process

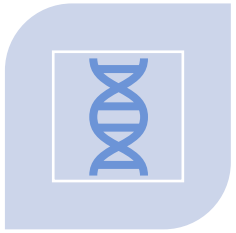
17 May 2021

FDA-CDER Efforts

PFDD MEETINGS

METHODOLOGIC
GUIDANCE DOCUMENTS

STANDARD CORE COA
GRANT PROGRAM



RARE DISEASE CURES
ACCELERATOR-DATA
ANALYTICS PLATFORM

INTERNATIONAL COUNCIL FOR HARMONISATION
PFDD REFLECTION PAPER

PFDD Meetings

Designed to engage patients and elicit their perspectives on two topic areas:

(1) the most significant symptoms of their condition and the impact of the condition on daily life;

(2) their current approaches to treatment.

In the past year, FDA conducted 3 PFDD me

- Stimulant Use Disorder
- Systemic Sclerosis
- Vitiligo

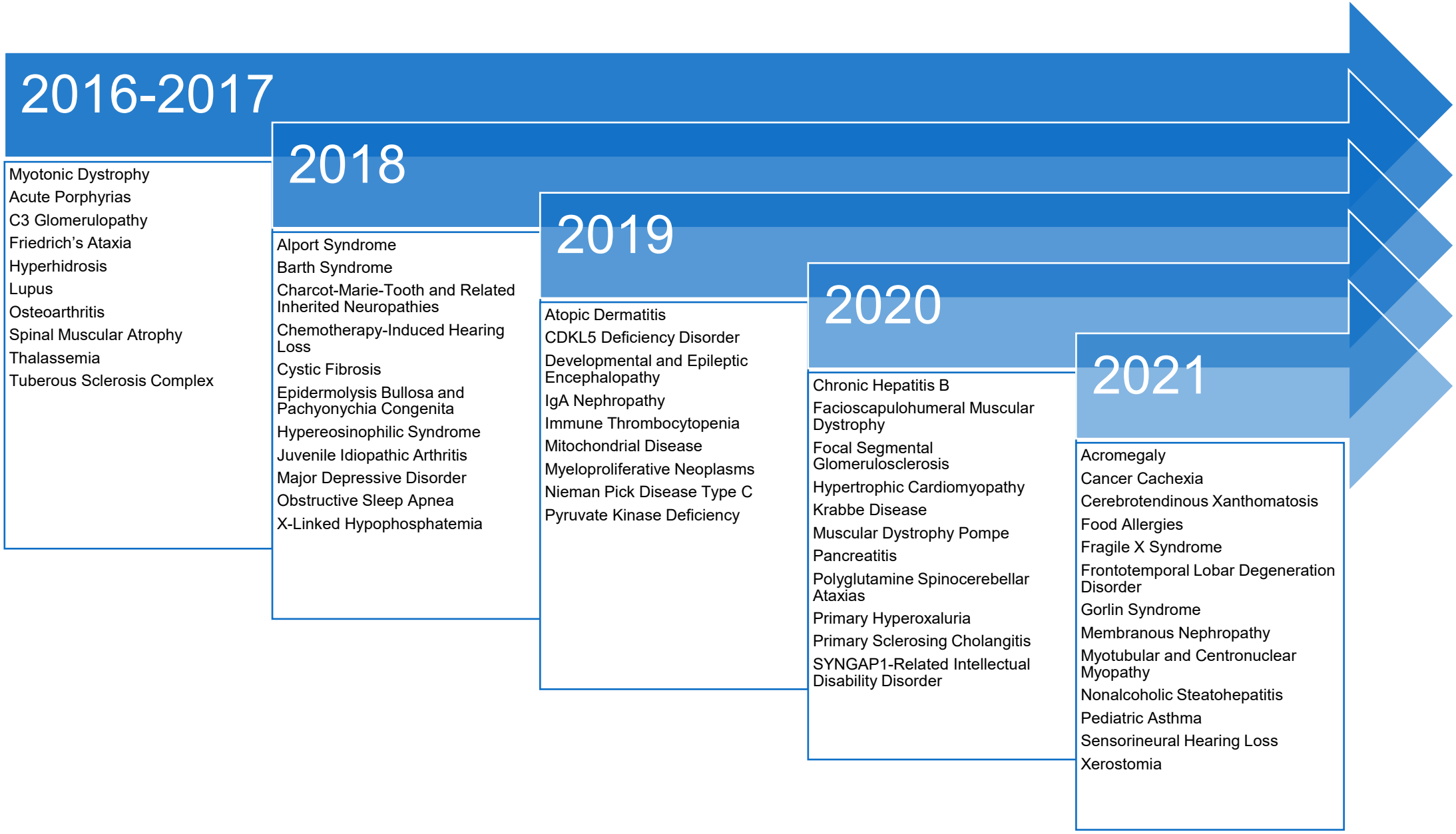
Externally-Led PFDD Meetings

In the past year, patient groups have conducted 13 EL-PFDD meetings

https://www.fda.gov/industry/prescription-drug-user-fee-amendments/fda-led-patient-focused-drug-development-pfdd-public-meetings

https://www.fda.gov/industry/prescription-drug-user-fee-amendments/externally-led-patient-focused-drug-development-meetings

Externally-Led Patient-Focused Drug Development Meetings



According to stakeholders, the meetings had **four main benefits:**

1. Hosts reported patients felt heard, supported, and empowered.

2. Stakeholders built relationships with each other.

3. Stakeholders confirmed their knowledge with real-world experiences.

4. Stakeholders learned about a new perspectives, component, or priorities related to the disease.

> It was a good **bonding experience** for the patients and families, and it had an impact on policy makers. (Host)

> By attending we **created relationships within the community** to hopefully provide [information about] the issue and what we are doing to hopefully address it. (Industry)

> Some of the information we already knew, and it was validated to see what was most important to [patients]. When it comes on the stage in aggregate from people there on the stage, audience, and on the phone as well, that was **helpful to know if we were going in the right direction** with our clinical design. (Industry)

> There were some areas and things that we heard about that were new for us and gave us the **opportunity to do additional follow-up** for a research question or finding that we had not thought about before. (Industry)

Example of PFDD in Reviews

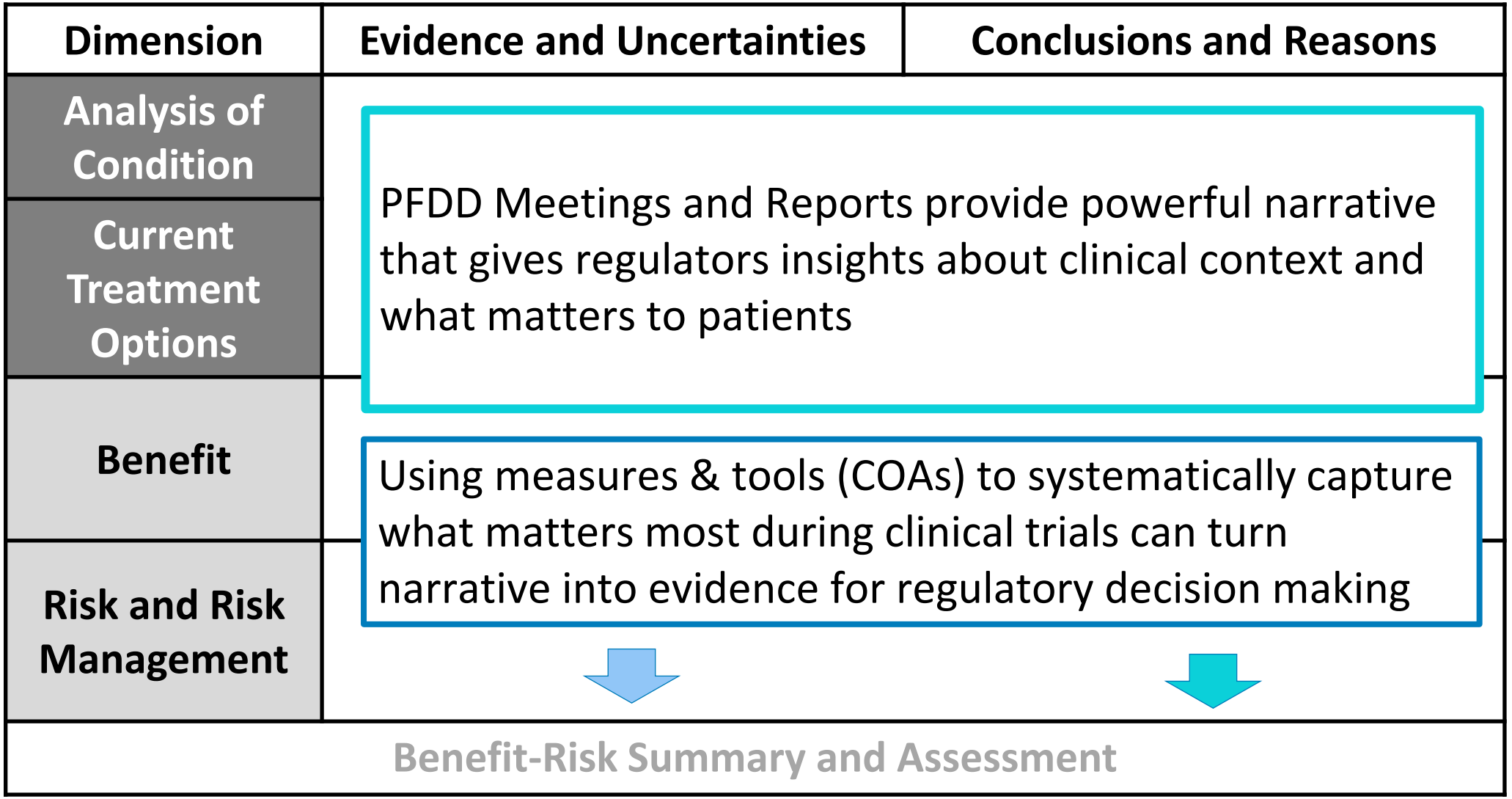
- Axillary Hyperhidrosis

  "During that meeting [EL-PFDD meeting held by the International Hyperhidrosis Society], some patients with axillary hyperhidrosis expressed that they could not qualify for clinical trials because they did not sweat sufficiently during the gravimetrically-measured sweat production assessment at screening. One patient in particular expressed that her sweating was not constant, but episodic. "

- Primary hyperoxaluria type 1 (PH1)

  "The review team also considered the experience and perspectives shared by patients and caregivers during an Externally-led Patient Focused Drug Development meeting hosted by the Oxalosis and Hyperoxaluria Foundation on October 5, 2020 and the publications listed in Table 4 **to inform the benefit-risk assessment**."

Series of Methodological Guidances to enable stakeholders to go beyond powerful narrative and collect data that can serve as study endpoints and be used as a basis for marketing decisions



Methodologic Guidance Documents

- Collecting Comprehensive and Representative Input
- Methods to Identify What is Important to Patients
- Selecting, Developing or Modifying Fit-for-Purpose Clinical Outcome Assessments
- Incorporating Clinical Outcome Assessments into Endpoints for Regulatory Decision Making

https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical

PFDD Guidance 1: Collecting Comprehensive and Representative Input

- Whom do you get input from, and why?
- How do you collect the information?

Status:

- Workshop held on December 18, 2017
- Issued Draft Guidance in June 2018 and Final Guidance in June 2020

Guidance 1

Guidance 2

Guidance 3

Guidance 4

Other

PFDD Guidance 2: Methods to Identify What is Important to Patients

- What do you ask, and why?
- How do you ask non-leading questions that are well-understood by a wide range of patients and others?

Status:

- Workshop held on October 15-16, 2018
- Issued Final Guidance in February 2022

PFDD Guidance 3: Select, Develop or Modify Fit-for-Purpose Clinical Outcome Assessments

- How do you decide what to measure in a clinical trial and select or develop fit-for-purpose clinical outcome assessments (COAs) ?

Status:

- Workshop held on October 15-16, 2018
- Discussion Document published

Guidance 1
Guidance 2
Guidance 3
Guidance 4
Other

PFDD Guidance 4: Incorporating Clinical Outcome Assessments into Endpoints for Regulatory Decision Making

- Once you have a COA measurement tool and a way to collect data using it, what is an appropriate clinical trial endpoint?

Status:

- Workshop held on December 6, 2019
- Discussion Document published

Developing and Submitting Proposed Draft Guidance Relating to Patient Experience Data

- How can a person seeking to develop and submit proposed draft guidance relating to patient experience data for consideration by FDA submit the proposed draft guidance?

Status:

- Workshop held on March 19, 2018
- Issued Draft Guidance in December 2018

Standard Core COA Grant Program

- Goal: Enable development of standard core sets of measures of disease burden and treatment burden for a given area—that would be made publicly available at nominal or no cost
- Currently funding 5 grants:
  - **Migraine** Clinical Outcome Assessment System (MiCOAS)
  - Clinical Outcome Assessments for **Acute Pain** Therapeutics in Infants and Young Children (COA APTIC)
  - Northwestern University Clinical Outcome Assessment Team (NUCOAT) – **Physical Function**
  - Preparing a Clinical Outcomes Assessment Set for Nephrotic Syndrome (Prepare-NS)- **Fluid Overload**
  - Expanding the Observer-Reported **Communication** Ability (ORCA) Measure

https://www.fda.gov/drugs/development-approval-process-drugs/cder-pilot-grant-program-standard-core-clinical-outcome-assessments-coas-and-their-related-endpoints

Rare Disease Cures Accelerator-Data Analytics Platform

INTENDED TO SERVE AS A NEUTRAL, INDEPENDENT DATA COLLABORATION AND ANALYTICS HUB TO PROMOTE THE SHARING OF CRITICALLY IMPORTANT DATA ACROSS RARE DISEASES IN ORDER TO ACCELERATE THE UNDERSTANDING OF DISEASE PROGRESSION.

GOAL TO ESTABLISH A DATA MANAGEMENT AND DATA REPOSITORY SYSTEM

HOUSE DATA FROM EXISTING AND PLANNED RARE DISEASE CLINICAL TRIALS AND NATURAL HISTORY STUDIES

https://www.fda.gov/drugs/regulatory-science-research-and-education/rare-disease-cures-accelerator

International Council for Harmonisation PFDD Reflection Paper

This Reflection Paper:

- identifies key areas where incorporation of the patient's perspective could improve the quality, relevance, safety and efficiency of drug development and inform regulatory decision making.
- presents opportunities for development of new ICH guidelines to provide a globally harmonized approach to inclusion of the patient's perspective in a way that is methodologically sound and sustainable for both regulated industry and regulatory authorities.

https://www.ich.org/page/reflection-papers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SESSION 6: ADDITIONAL PATHWAYS TO INTERACT WITH FDA CDER

CLOSING REMARKS

Kerry Jo Lee, MD

Associate Director for Rare Diseases

Division of Rare Diseases and Medical Genetics

CDER, FDA

CLOSING REMARKS

Philip John (PJ) Brooks, PhD

Acting Director

Division of Rare Diseases Research Innovation

National Center for Advancing Translational Sciences, NIH

ADJOURNMENT

REGULATORY FITNESS IN RARE DISEASE CLINICAL TRIALS

A Workshop by the
FDA's Center for Drug Evaluation & Research and
NIH's National Center for Advancing Translational Sciences

May 16-17, 2022