Challenges and Commitments to Drug Development for Rare Diseases, a Regulatory Perspective

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Disclosure Statement

- No conflicts of interest
- Nothing to disclose
- This talk reflects the views of the author and should not be construed to represent FDA's views or policies
- In this talk "drug" refers to both drugs and biologics

Welcome from the FDA and DGIEP

Overview

- FDA Mission and DGIEP Commitments
- Drug Development Considerations
  - Rare disease challenges
  - Mandates and flexibility
  - Patient Focused Drug Development
  - Orphan Drug Act, Pediatric Rare Disease, and Resources

FDA Mission

The Food and Drug Administration is responsible for protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices.

DGIEP Commitments

- Our ultimate stakeholders are patients and their families
- Our mission is to get safe and effective drugs for rare diseases with serious unmet medical needs to the market in as expeditious a manner as possible
- We encourage innovative trial designs supported by science with the ability to advance development for promising therapies
- Enhanced understanding of each disease and the patients' experience can facilitate creative approaches to drug development
- We highly value the ability to partner with patient groups, the academic community, therapeutic developers, and other regulatory agencies
  - *"Coming together is a beginning; keeping together is progress; working together is success."*- Henry Ford

Rare Diseases

- 1 in 10 Americans have a rare disease (~30 million)
  - Over 7,000 identified rare diseases
- Most rare diseases are serious and progressive, many are fatal, and few have an FDA approved treatment
  - Of the 7000 known rare diseases, ~500 have approved therapies (7%)
- 85% are genetic, 50% affect children

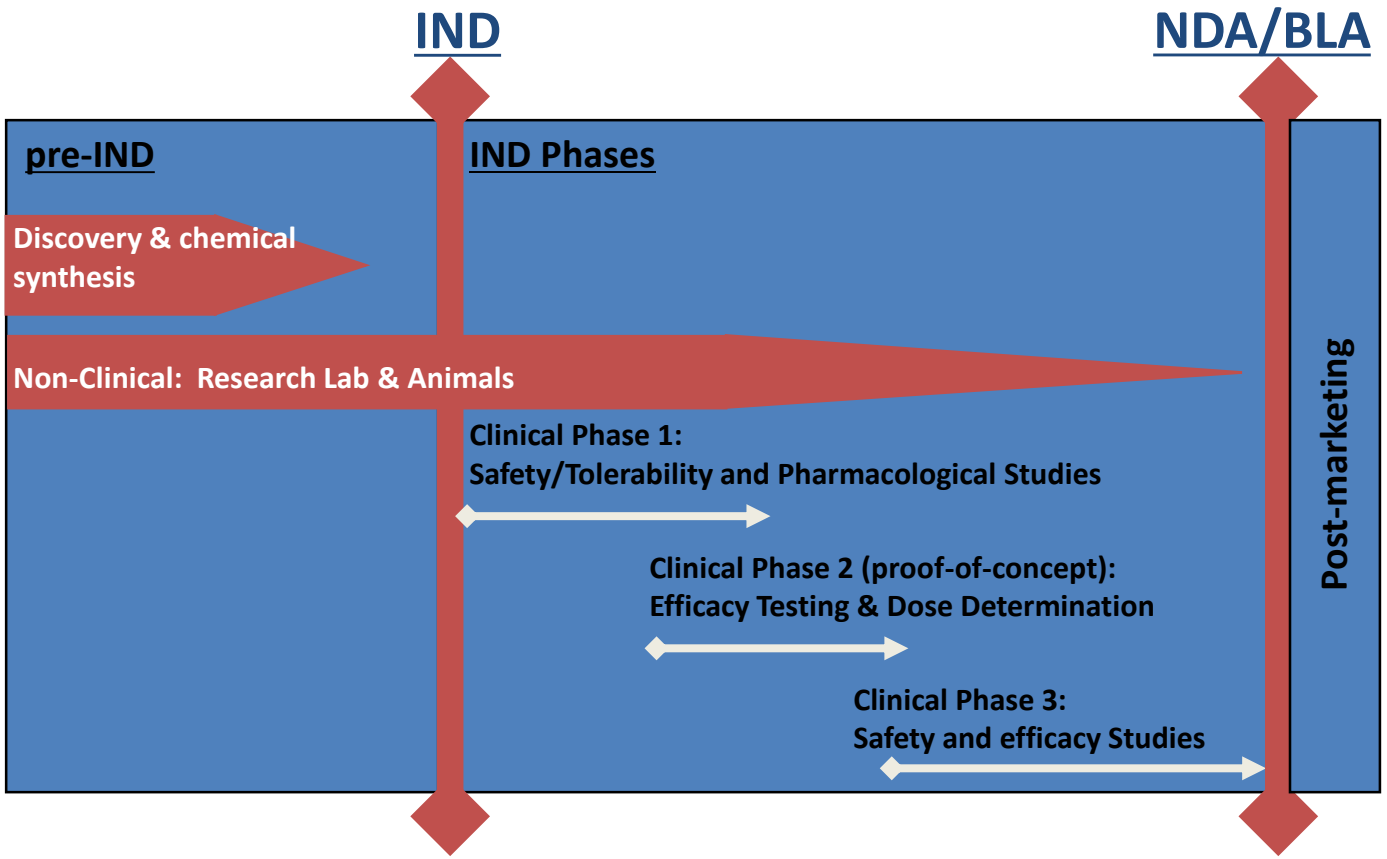
Challenges

- Lack of regulatory/drug development precedent
- Rare diseases with few patients available to participate
  - Multi-center, multi-country trials
- Diverse phenotypes, genetic subsets
  - Heterogeneity at presentation / late diagnosis
  - Highly variable disease course
- Pediatric and adult populations
- Natural histories are often not well understood/characterized
- Conditions may be chronic, progressive, serious, life-limiting, and life-threatening with unmet medical need
- Well defined endpoints, outcome assessments, and/or biomarkers may not be available

Rare Pediatric Diseases

- About **50% of rare disease patients are children**
- Pediatric research studies should pose **no more than minimal risk** or the risk needs to be justified by anticipated benefit (prospect of direct benefit)
- Need to rely on parents to consent
- Children need to provide **ongoing assent**
- Need to incorporate pediatric patients early on in drug development

Drug Development Paradigm



What is the Same

- Statutory standards for approval apply to all drugs including those for rare diseases
- Best access for patients to effective, safe, and quality treatments is through approved drugs
  - Investigational agents do not yet have safety and efficacy characterized
- Ethical and safety standards remain
  - Patients with rare diseases deserve the same protections

21 CFR 314.50
21 CFR 314.126
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072008

Evidentiary Standard for Approval

- Regulatory Requirement:
  - Demonstrate **substantial evidence of effectiveness/clinical benefit**[1]
- Substantial evidence of benefit requires a*dequate and well-controlled clinical studies*[2]
    - Usual approval standard is two adequate and well-controlled studies (affirm and confirm)

[1]21CFR 314.50
[2]21CFR 314.126

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Adequate and Well-Controlled

- Trial has been designed well to be able to "distinguish the effect of a drug from other influences, such as spontaneous change…, placebo effect, or biased observation"
  - Includes comparison of active treatment with a control
    - Placebo concurrent
    - Dose-comparison concurrent
    - No treatment concurrent
    - Active treatment concurrent
    - Historical control
      - » diseases with high and predictable mortality or in which the effect of the drug is self evident

21 CFR 314.126

Regulatory Flexibility in Demonstrating "Substantial Evidence" of Effectiveness

- FDA Modernization Act (FDAMA), 1997 provided a complimentary statutory standard for demonstration of substantial evidence of effectiveness
  - If [FDA] determines, based on relevant science, that data from **one adequate and well-controlled clinical investigation and confirmatory evidence** (obtained prior to or after such investigation) are sufficient to establish effectiveness, [FDA] may consider such data and evidence to constitute substantial evidence

21 CFR 312.80
21 CFR 314.105(c)

Use of FDA Approval "Flexibility"

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

	Orphan Drug	Non-Orphan
≥ 2 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 Adequate and Well-Controlled Studies)	29%	72%
"Flexible Approval" (Accelerated Approval and/or Approval Based on < 2 Adequate and Well-Controlled Studies)	71%	28%

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IEM Regulatory Review

Examples of Recent Approvals

- Palynziq
  - Approved May 24, 2018 to reduce blood phenylalanine concentrations in adult patients with phenylketonuria who have uncontrolled blood phenylalanine concentrations greater than 600 micromol/L on existing management.
    - Patroula Smpokou, *FDA/CDER/DGIEP*
    - Holly Weng, *BioMarin Pharmaceutical*
- Brineura
  - Approved April 27, 2017 to slow the loss of ambulation in symptomatic pediatric patients 3 years of age and older with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2), also known as tripeptidyl peptidase 1 (TPP1) deficiency.
    - Elizabeth Hart, *FDA/CDER/DGIEP*
    - David Jacoby, *BioMarin Pharmaceutical*
- Mepsevii
  - Approved November 15, 2017 in pediatric and adult patients for the treatment of Mucopolysaccharidosis VII (MPS VII, Sly syndrome).
    - Dina Zand, *FDA/CDER/DGIEP*
    - Qais Abu Ali, *Ultragenyx*

Patient-Focused Drug Development

- 21st Century Cures Act, December 2016
  - Issue guidances describing how FDA anticipates incorporating relevant patient experience data and related information into the structured benefit-risk assessment framework to inform regulatory decision-making
- 2017 FDA Reauthorization Act (FDARA), Title I (PDUFA VI)
  - Enhance the incorporation of the patient's voice in drug development and decision-making
- Patient-Focused Drug Development Draft Guidances
  - Set of four documents in development
  - https://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm610279.htm

Patient-Focused Drug Development (PFDD)

- Primary goal- To better incorporate the voice of the patient into drug development and evaluation
  - Collecting and utilizing patient and caregiver input
  - Facilitate enrollment and minimize patient burden
  - Capture information of patient preferences and acceptability of tradeoffs between benefit and risk
  - Identify the information that is most important to patients
- Challenges
  - Developing and validating clinical outcome assessments (*i.e.,* patient reported, observer reported) in small populations across multinational studies
  - Highly sensitive to bias
    - Importance of adequate randomization and blinding

Orphan Drug Act

- Provides incentives intended to make the development of drugs to treat small populations financially viable
  - Seven years of marketing exclusivity
  - Waiver of PDUFA fees
  - Tax credits for up to 25% of qualified clinical trial costs
  - Orphan Grant Program
- Does not define standard for approval; does not define lower or different standards for development or approval for orphan drugs
- Orphan drug designation
  - Separate process and considerations from IND/NDA submissions
  - Need to specifically apply for Orphan Designation prior to NDA/BLA filing
- For more information, please contact the Office of Orphan Products Development: https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/default.htm

Rare Pediatric Disease Priority Review Voucher Program

- Created under section 908 of FDASIA to encourage development of drugs and biologics for rare pediatric diseases
  - Section 529 of the Food, Drug, & Cosmetic Act, July 1012
- Upon marketing approval, the sponsor for a RPD drug may be eligible for a voucher redeemable for a 6-month priority review for a subsequent marketing application that would have otherwise received a 10-month standard review

Definitions

- **“Rare Pediatric Disease”**
  - Revised by the Advancing Hope Act of 2016
  - “a serious and life-threatening disease in which the **serious or life-threatening manifestations** primarily affect individuals aged from birth to 18 years”
  - Must be a rare disease (200,000 or fewer persons in the US)
- **“Rare Pediatric Disease Product Application”**
  - New Molecular Entity
    - Contains no active ingredient (including any ester or salt of the active ingredient) that has been previously approved
  - Eligible for priority review
  - Relies on clinical data from studies in a pediatric population
  - Does not seek approval for an adult indication in the original rare pediatric disease product application

The Process

- Consists of 2 components
  - **Designation as a "rare pediatric disease"**
    - May apply for designation at the same time as orphan designation or fast-track designation (these requests should be submitted as separate proposals)– 60 day clock for review
    - Voluntary
    - Not a pre-requisite to be eligible for a PRV
    - Reviewed by the Office of Orphan Product Development and Office of Pediatric Therapeutics
  - **Voucher eligibility determination**
    - Whether NDA or BLA satisfies criteria for a "rare pediatric disease application"
    - Sponsor must request priority review voucher at the time the application is submitted regardless of designation status
    - Presence of designation does not guarantee that the product is eligible for the program
- As of September 2018
  - 15 rare pediatric vouchers have been awarded
  - 7 have been redeemed for priority reviews
- Draft Guidance for Industry Rare Pediatric Disease Priority Review Vouchers
  - https://www.fda.gov/RegulatoryInformation/Guidances/ucm423313.htm

Additional Resources

- FDA CDER Office of New Drugs, Rare Diseases Program
  - https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm221248.htm
- Expedited Programs for Serious Diseases
  - Fast Track, Breakthrough, Priority Review designations, and Accelerated Approval pathway
  - Guidance: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf
- Draft Guidance for Industry Rare Diseases: Common Issues in Drug Development
  - https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM458485.pdf
- Draft Guidance for Industry Inborn Errors of Metabolism That Use Dietary Management: Considerations for Optimizing and Standardizing Diet in Clinical Trials for Drug Product Development
  - https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM614252.pdf

Additional Resources

- Draft Guidance for Industry Pediatric Rare Diseases – A Collaborative Approach for Drug Development Using Gaucher Disease as a Model
  - http://sharepoint.fda.gov/orgs/CDER-CommunicationsforGuidanceDocuments/Shared%20Documents/Pediatric%20Rare%20Diseases--A%20Collaborative%20Approach%20for%20Drug%20Development%20Using%20Gaucher%20Disease%20as%20a%20Mo.pdf
- Draft Guidance for Industry Slowly Progressive, Low-Prevalence Rare Diseases with Substrate Deposition That Results from Single Enzyme Defects
  - http://sharepoint.fda.gov/orgs/CDER-CommunicationsforGuidanceDocuments/Shared%20Documents/Slowly%20Progressive,%20Low-Prevalence%20Rare%20Diseases%20with%20Substrate%20Deposition%20That%20Results%20from%20Single%20.pdf
- Guidance for Industry Nonclinical Safety Evaluation of Pediatric Drug Products
  - http://sharepoint.fda.gov/orgs/CDER-CommunicationsforGuidanceDocuments/Shared%20Documents/Nonclinical%20Safety%20Evaluation%20of%20Pediatric%20Drug%20Products.pdf
- Many others currently in development

In Closing

- The work you are doing is important and valued
- Take advantage of opportunities for formal meetings
  - Guidance for Industry, Formal meetings between the FDA and sponsors or applicants
    - https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM590547.pdf
  - Critical Path Initiative Meetings
    - http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformion/Guidances/UCM417627.pdf
  - Biomarker Qualification Program
    - https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/BiomarkerQualificationProgram/ucm535383.htm
  - Patient Affairs Staff
    - https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/ucm589472.htm
- We want to partner with you to bring safe and effective therapies to those in need


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ADDITIONAL FDA RESOURCES (for reference)

Fast Track

- Expedited program for products with potential to address unmet need
- Qualifying criteria - includes a serious condition and a drug's potential to fulfill an unmet medical need
- Benefits – allows for early and frequent interaction with the review team; rolling submissions

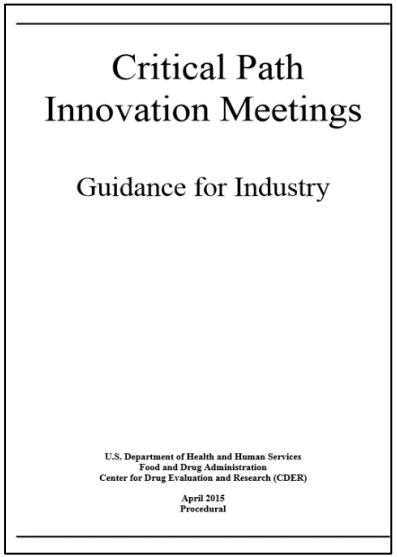
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf

Breakthrough Therapy

- Expedited program for products with potential to address unmet need
- Qualifying criteria - includes a serious condition and preliminary clinical evidence of substantial improvement over existing therapies on one or more clinically significant endpoints
- Benefits – intensive guidance on efficient drug development, organizational commitment, rolling review, other actions to expedite review

http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf

Critical Path Innovation Meetings (CPIM)



- http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformion/Guidances/UCM417627.pdf

- Discussion of the science, medicine, and regulatory aspects of innovation in drug development
- Nonbinding meeting
- 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

BEST Resource

- A glossary of terminology and uses of biomarkers and endpoints in basic biomedical research, medical product development, and clinical care
- BEST harmonizes terms and definitions and addresses nuances of usage
- Created by the NIH-FDA Biomarker Working Group
- Publicly available at: http://www.ncbi.nlm.nih.gov/books/NBK326791/
- Email biomarkers@ncbi.nlm.nih.gov

Biomarkers

- A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions:
  - **Types**: Molecular, histologic, radiographic, or physiologic characteristics are types of biomarkers
  - **Examples**: blood glucose (molecular), biopsy-proven acute rejection (histologic), tumor size (radiographic) and blood pressure (physiologic)

Biomarker Qualification Process

- Establishes the use of a biomarker for a specific context of use in drug development and makes information publicly available
- Qualification is a regulatory conclusion that means a biomarker:
  - Has adequate data to support the qualified context of use in drug development
  - Has evidence that supports the potential benefit for its use in clinical trials to aid in developing new therapeutics
  - Can be used in any drug development program under the qualified context of use
  - Has qualification recommendations and FDA review documentation publicly available on the Biomarker Qualification Program's website

Biomarker Qualification Process

- Biomarker qualification is a tool for drug development and **not for approval/clearance of diagnostics or for companion diagnostics for use in clinical practice**
- **Requestor** can be a person, a group, organization (including the federal government), or consortium that takes responsibility for and initiates a BQ proposal using the procedures described in the DDT guidance
- **No fees** for submissions to the BQ program
- Biomarker qualification is **voluntary**
- Once qualified for a specific **context of use**, a biomarker can be used by drug developers for other applications for the qualified context, without re-review
- Biomarkers considered for qualification are conceptually **independent of the specific test or device** performing the measurement

https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/BiomarkerQualificationProgram/ucm535383.htm

Clinical Outcome Assessments to Assess how Patients "Feel" or "Function"

The FDA encourages the development and implementation of patient-focused clinical outcome assessments (COAs) in clinical trials to support drug approvals and labeling claims.

Clinical outcome assessment (COA) can be made through report by a clinician, a patient, a non-clinician observer (e.g., caregiver) or through a performance-based assessment. There are four types of COAs:

- **Clinician-reported outcome**
- **Observer-reported outcome**
- **Patient-reported outcome**
- **Performance outcome**

- **FDA COA Staff Website: http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm349031.htm#Endpoints**
- **COA Qualification Website: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284077.htm**
- **COA Compendium Website: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm459231.htm**
- **PRO Guidance (2009): http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf**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