Defining and Assessing Clinical Benefit: A Regulatory Perspective

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Overview

- Defining clinical benefit
  - Definitions
  - Challenges
  - Mandates
  - Flexibility
- Assessing clinical benefit
  - Patient Focused Drug Development
  - Endpoints
    - Clinical outcome assessments
    - Surrogate endpoints
    - Biomarkers

General Definitions and Background

- Rare disease: condition that affects < 200,000 people in US
- 1/10 have a condition that is considered a rare disease
  - 85% genetic, 50% affect children
- Most rare diseases are serious, progressive, life threatening
- Few have an FDA approved treatment
  - Of ~7000 known rare diseases, ~500 have approved therapies (7%)
- ~1/2500 have a mitochondrial disorder
  - About 1/4000 affect children

Orphan Drug Act
Omim.org

The Challenges

- Small population
- Heterogeneous population, even within the same genotype
- Pediatric and adult populations
- Natural histories are often not well characterized, subject to bias, which can lead to difficulties in matching and analysis
- Need for early intervention, particularly urgent if disorder has high morbidity/mortality
- Lack of validated clinical outcomes assessments
- Lack of well-defined clinically meaningful endpoints
- Lack of precedent

Evidentiary Standard for Approval

- Substantial evidence of effectiveness/clinical benefit[1]
  - Typically: Requires **two** a*dequate and well-controlled clinical studies*[2] Studies that have been designed 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 assignment of subjects to treatment and control
    - Appropriate selection of subjects
    - Adequate measures to minimize bias
    - Well-defined and reliable methods of assessing response
    - Prospectively planned analyses designed with rigor

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

Regulatory Flexibility

- FDA Modernization Act (FDAMA), 1997
  - 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.

- Regulatory flexibility
  - FDA can "exercise its scientific judgment" in determining the kind and quantity of data a sponsor is required to provide for individual drug development programs

21 CFR 312.80
21 CFR 314.105(c)

Patient-Focused Drug Development

- Primary goal: *incorporate the patient voice*
  - FDA Reauthorization Act (FDARA), Title I (PDUFA VI), 2017
  - 21st Century Cures Act, 2016
    - Guidances incorporating patient experience into the benefit-risk assessment to inform regulatory decision-making
  - Mitochondrial diseases are often multisystemic, heterogeneous
    - Clinical meaningfulness

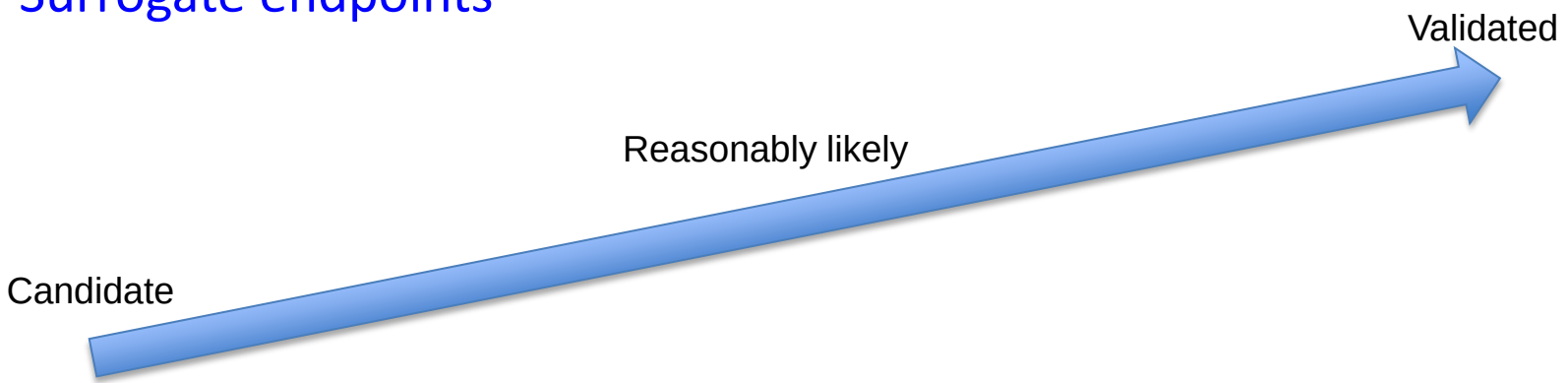
Patient Focused: Assessing Efficacy

- Evidence that treatment has a positive impact on: "***FEELS, FUNCTIONS, or SURVIVES"****
  - How a patient feels or functions in daily life: Clinical Outcome Assessments (COAs):
    - Patient-Reported Outcomes (PROs)
    - Clinician-Reported Outcomes (ClinROs)
    - Observer-Reported Outcomes (ObsROs)
    - Performance Outcomes (PerfOs)
  - Clinical Benefit/Survival
- Challenges
  - Validating and standardizing COAs and other endpoints in small populations and across multinational studies
  - Sensitive to bias
    - Importance of adequate randomization and blinding

*Thurgood Marshall. US v Rutherford 1979; Preamble to the accelerated approval rule (1992).

Assessments in Efficacy:
"FEELS, FUNCTIONS, or SURVIVES"

- Types of endpoints
  - Clinical Outcomes
    - Examples: symptom diary (feels), 6MWT (functions), survival
  - Surrogate endpoints



  - Biomarkers
    - Objective measurement
    - Examples: Brain MRI, EKG, Plasma amino acids, Lactate

https://www.fda.gov/drugs/development-resources/surrogate-endpoint-resources-drug-and-biologic-development

Summary

- Multiple unique challenges
- Flexibility to aid in accelerated development
- Committed to tailor efficacy to match the patient's voice
- Resources:
  - 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
  - Biomarker Qualification Program: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/BiomarkerQualificationProgram/ucm535383.htm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