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
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 adequate 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

Assessments in Efficacy: “FEELS, FUNCTIONS, or SURVIVES”

- Types of endpoints
  - **Clinical Outcomes**
    - Examples: symptom diary (feels), 6MWT (functions), survival
  - **Surrogate endpoints**
    - Validated
      - Reasonably likely
        - Candidate
    - **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