Approach to Clinical Trials in Drug Development: Eosinophilic Esophagitis (EoE)

Preeti Venkataraman, M.D.
Division of Gastroenterology & Inborn Errors Products (DGIEP)
Center for Drug Evaluation and Research (CDER)
U.S. Food & Drug Administration (FDA)

The views expressed in this presentation are those of the speaker and not necessarily of the FDA.

Outline

• Review the importance of selecting endpoints that constitute clinically meaningful signs and symptoms of the disease

• Emphasize how adequate characterization of natural history of a disease is paramount to trial design and selecting appropriate endpoints

Outline

• Review the level of evidence required to support drug approval
  – Discuss need for clinically meaningful endpoints (“keeping the focus on the patient”)

• Discuss the role of surrogate endpoints in drug approval and relevance to EoE
• 1962 Drug Amendments to the FDC Act require establishment of "substantial evidence" of effectiveness of the drug as a prerequisite for marketing approval
  
  – "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…"

What Constitutes Effectiveness?

• Food, Drug and Cosmetic Act does not directly state what endpoints provide evidence of effectiveness

• "Clinically Meaningful Endpoint" …a direct measure of how a patient "functions, feels or survives." —Robert Temple, FDA

• Accelerated Approval: Rely upon surrogates reasonably likely to predict clinical benefit.
  - Subpart H - drugs (21 CFR 314)
  - Subpart E – biologics (21 CFR 601)

• Treatment Benefit
  - The impact of treatment on how a patient survives, feels, or functions

  VS.

• Surrogate Endpoints
  - Do not directly describe how a patient feels, functions, or survives as a result of treatment
What is a Surrogate Endpoint?

- A measurement or a physical sign used as a substitute for a clinically meaningful endpoint that measures directly how a patient feels, functions, or survives.

Approval based on Surrogate Endpoints

1. Surrogate endpoints can be used for a “regular” approval
   - e.g., blood pressure, HIV-1 RNA, HbA1c
2. Surrogate endpoints that support Accelerated approval are different:
   - reasonably likely to predict clinical benefit

Accelerated Approval Regulations and Surrogates

- Provide for reliance on a “surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit.” [21 CFR 314 & 601]
- Requires further study of drug “to verify and describe clinical benefits” associated with the product.
Currently No FDA-Approved Drugs for EoE Indication

Challenges to Drug Development

- Esophageal eosinophils currently inadequate as a surrogate endpoint to predict clinical benefit
  - Symptoms and endoscopic features do not always correlate with esophageal eosinophilia.
- No validated symptom assessment tool to measure disease severity and treatment response

Challenges to Drug Development, cont.

- Paucity of data on the natural history of EoE
- Small population with the disease
- Phenotypic diversity adds to complexity
Natural History Studies for EoE

• Improved understanding of natural history & symptomatology ⇒ better endpoint selection & PRO development

Natural History Studies for EoE

➢ Importance of understanding natural history of EoE to inform study design, study population and endpoints
  ➢ “Begin with the end in mind”
  ➢ Ideally we would have full & complete understanding of EoE natural history
  ➢ Different EoE “phenotypes”: may exhibit different symptoms and natural histories ⇒ therefore may require different study designs/study populations
  ➢ Pediatrics vs. adults: Extrapolation of efficacy may be dependent on the specific phenotype
  ➢ Understand the natural history of both the disease itself AND the symptoms…and their relationship

Surrogates & EoE

• At present, it appears that no surrogate can be used as the basis for either regular approval or accelerated approval of drugs for EoE. ...Why not?

• For Regular Approval: The quantitative relationship between the surrogate and a clinical outcome has not been established ⇒ i.e., a surrogate has not been “validated”

• For Accelerated Approval: Not clear at this time what surrogate is reasonably likely to “predict” a clinical benefit
Clinical Trial Design Elements

• Before initiating clinical trials intended to support marketing approval, it is critical to:
  – Understand the natural history of EoE disease progression early in development.
  – Design early phase trials to:
    • determine the appropriate dose
    • determine timing of assessments
    • develop clinical outcome assessments
    • inform design of efficacy trial(s) that will support approval.

Types of Endpoint Measures of Clinical Benefit for Regular Approval

• Survival
• Feels/Functions: Clinical outcome assessments (COAs)
  – Patient-reported outcomes (PROs)
  – Clinician-reported outcomes (ClinROs)
  – Observer-reported outcomes (ObsROs)
  – Performance outcomes (PerfOs)

Patient-Reported Outcome (PRO) Assessment

• An assessment based on a report that comes directly from the patient without interpretation.
• Can be self-completed or interviewer-administered.
• PRO assessments can measure patient’s symptoms, signs, or an aspect of functioning related to a disease.
• Only PRO assessments can measure symptoms a patient experiences with a condition.
• Example:
  – Self-report of pain intensity on a 0 to 10 numeric rating scale (NRS)
• FDA’s PRO Guidance
Clinical Outcome Assessments

- Ongoing development of Clinical Outcome Assessments (COAs)
- There are a number of COAs currently in development
- Validating COAs/PROs is not easy but it is the clearest path forward to identifying clinically meaningful endpoints
- Concerns over ability of COAs to address patient modifying behavior, placebo effects, different phenotypes, etc.

Avenues of Research

- Biomarkers
  - Possible role in prognosis, pharmacodynamic response to treatment and identifying new drug targets but not yet as surrogate endpoints for approval in EoE
- Endoscopic & Histologic Scores
  - Role in clinical studies: Could provide evidence of an impact on disease (and not just improvement of symptoms)

Conclusion

- Understanding natural history is critical to defining a disease, identifying clinically meaningful endpoints, and designing adequate & well-controlled trials
- Qualifying a PRO (COA) for adult and pediatric studies is critical to developing drugs to treat EoE.
- Academia, industry and regulatory bodies will need to work together to make this all happen.
Acknowledgements

- Julie Beitz, MD
- Donna Griebel, MD
- Andrew Mulberg, MD
- Elektra Papadopoulos, MD

Thank You

Back Up Slides
Measurement Properties

- Content Validity
  - Critical for interpretation and labeling
  - Should be established prior to evaluating other measurement properties

- Construct Validity:
  - Evidence that the PRO concepts measured conform to a priori hypotheses concerning expected relationships with other measures or characteristics of patients/patient groups

- Reliability
  - Test-retest: Stability of scores over time when not change expected in the concept of interest
  - Internal Consistency: Inter-correlation of items that contribute to a score

- Ability to detect change
  - Evidence that the PRO instrument can identify differences in scores over time (individual or group) who have changed with respect to measurement concept

Good Measurement Principles

- Defines good measurement principles to consider for “well-defined and reliable” (21 CFR 314.126) PRO measures intended to provide evidence of treatment benefit

- All COAs can benefit from the good measurement principles described within the guidance

References

- Code of Federal Regulation
  - Documented by “Substantial evidence” (21 CFR 201.56(a)(3))
  - Evidence from “Adequate and well-controlled clinical trials” (21 CFR 314.126)
  - The methods of assessment of subject’s response are “well-defined and reliable” (21 CFR 314.126)

- FDA Guidance Documents

- FDA’s COA Qualification Program Webpage