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

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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

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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

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- 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…"

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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)

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- **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

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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.

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Approval based on Surrogate Endpoints

1. Surrogate endpoints can be used for a "regular" approval
   - e.g., blood pressure, HIV-1 RNA, HbA_{1c}
2. Surrogate endpoints that support Accelerated approval are different:
   - reasonably likely to predict **clinical benefit**

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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.

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Currently No FDA-Approved Drugs for EoE Indication

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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

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Challenges to Drug Development, cont.

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

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Natural History Studies for EoE

- Improved understanding of natural history & symptomatology ➔ better endpoint selection & **PRO development**

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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

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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

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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.

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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)

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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
  - http://www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf

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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.

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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)

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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.

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Thank You

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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: Intercorrelation 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

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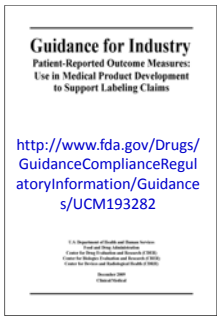
Good Measurement Principles


Guidance for Industry
Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282

- 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

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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

- US Food and Drug Administration. Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims Development Tools. December 2009. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf.

FDA's COA Qualification Program Webpage

- http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284077.htm

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