Drug Development in Inflammatory Bowel Disease: The FDA Perspective

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Disclosure

- Kerry Jo Lee, MD: Nothing to disclose
- The views expressed in this presentation are my own and not necessarily those of the FDA
Objectives

1. To review the key elements of the drug development process
2. To define clinical benefit and clinical outcome assessments used in clinical trials
3. To discuss the efficacy endpoints utilized in clinical trials for inflammatory bowel disease (IBD).
DRUG DEVELOPMENT PROCESS
New Drug Development Process

**IND Phases**

**pre-IND**
- Discovery & chemical synthesis

**IND Phases**
- Non-Clinical: Research Lab & Animals
- Clinical Phase 1: Safety/Tolerability and Pharmacological Studies
- Clinical Phase 2 (proof-of-concept): Early Efficacy Testing & Dose Determination
- Clinical Phase 3: Safety and efficacy Studies

**IND**

**NDA/BLA**

**Post-marketing**
Statutory Requirements for New Drug Approval

An approved drug must meet each of the following statutory requirements:

- Substantial evidence of effectiveness for treatment of the proposed indication
- Benefits for proposed population outweigh risks
- Manufacturing that ensures product identity, strength, quality (purity)
- Evidence-based drug labeling that adequately guides providers and patients to use the drug safely and effectively

What is “Substantial Evidence”?

• Section 505(d) of the FD&C Act:

“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, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.”
How Do We Demonstrate “Substantial Evidence”

• Demonstration of **substantial evidence** of effectiveness requires that studies are designed well enough “to distinguish the effect of a drug from other influences, such as spontaneous change... placebo effect, or biased observation”

• Adequate and well-controlled trials have:
  - Clear statement of purpose
  - Appropriate control for valid comparison
  - Appropriate selection of subjects
  - Appropriate assignment of subjects to treatment and control
  - Adequate measures to minimize bias
  - Well-defined and reliable methods of assessing response
  - Prospectively planned analyses designed with rigor

• Usually two adequate and well-controlled studies are required to support approval.

21CFR 314.50 and 21CFR 314.126
DEFINING CLINICAL BENEFIT AND ITS ASSESSMENT
Defining Clinical Benefit

- Clinical benefit is a favorable effect on a meaningful aspect of how a patient *feels* (e.g., symptom relief), *functions* (e.g., improved mobility) or *survives* as a result of treatment.

- Clinical benefit may be measured as an improvement or delay in the progression of a disease or condition (as manifested by how a patient feels/functions).

- Can be measured directly or indirectly.

- Indirect assessment needs justification for its value as a replacement for how patients survive, feel or function.

- Observed clinical benefit is described in labeling as a claim using words that represent the concept measured (should be meaningful and understandable to prescribers and patients).
Types of Clinical Outcome Assessments (COAs)

- **Patient-reported outcomes (PROs)**
  - Report of the status of a patient’s health condition that comes directly from the patient, without interpretation of the patient’s response by a clinician or anyone else (e.g., # of stools, pain)

- **Clinician-reported outcomes (ClinROs)**
  - Observations during examination (e.g., endoscopy results)

- **Observer-reported outcomes (ObsROs)**
  - Report based on observations

- **Performance outcomes (PerfOs)**
  - Defined tasks demonstrating functional performance in a clinical setting
Selecting the COA type

Context of use  Concept(s) of interest

Consider appropriateness of COA type

Unobservable concepts (e.g., feelings)

Observable concepts (e.g., signs, events, behaviors)

- Clinical judgment needed
- No clinical judgment needed

PRO
ClinRO

Self-report?
Yes
No

PRO
ObsRO
PerfO

Functional performance
DRUG DEVELOPMENT CONSIDERATIONS IN IBD
Drug Development in Crohn’s disease and ulcerative colitis

Co-primary efficacy endpoints in IBD clinical trials measure by:

- PRO: key signs and symptoms
- ClinRO: Scoring indices for endoscopic assessment in IBD clinical trials
The *ideal* primary efficacy assessment tool used in clinical trials to support marketing approval would consist of:

- A signs and symptoms assessment scale, best measured by a patient-reported outcome instrument and
- An endoscopic and histological assessment scale, best measured by a clinician-reported outcome instrument.
Ulcerative colitis (current approach)

• PRO: Key signs/symptoms (e.g. stool frequency and rectal bleeding)

• ClinRo: Endoscopy, measured by a Mayo Sub-score
Recommended Modifications to the Mayo Sub-score for Endoscopy in UC

**STANDARD MAYO SUBSCORE***

0 = Normal or inactive disease  
1 = Mild disease (erythema, decreased vascular pattern, mild friability)  
2 = Moderate disease (marked erythema, absent vascular pattern, friability, erosions)  
3 = Severe disease (spontaneous bleeding, ulceration)

**MODIFIED MAYO SUBSCORE**

0 = Normal or inactive disease  
1 = Mild disease (erythema, decreased vascular pattern, mild friability)  
2 = Moderate disease (marked erythema, absent vascular pattern, friability, erosions)  
3 = Severe disease (spontaneous bleeding, ulceration)

The modified version does not include friability in the score of 1.

Crohn’s Disease (current approach)

- **PRO:** Key signs/symptoms (e.g. abdominal pain, liquid/watery stool frequency)

- **ClinRo:** Endoscopy, measured most commonly by SES-CD
Endoscopic Assessment in Crohn’s Disease

• Historically, endoscopy was not used to evaluate efficacy in clinical trials for Crohn’s disease

• Challenges with historical approach
  – Signs and symptoms of Crohn’s disease can overlap with other GI diseases\(^1\)
  – CDAI is poorly correlated with intestinal inflammation\(^2\)

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\(^2\) Colombel, JF et al. Converging goals of treatment of Inflammatory Bowel Disease from clinical trials and practice. Gastroenterology 2015; 48:37-51
SES-CD

- Simple Endoscopic Score for Crohn’s Disease
- Scores range from 0-56
- Affected surface subscore: % of surface covered by “any other lesions”

SES-CD: Future challenges

- Unexplored segments are considered free of disease
- Disease severity can be underestimated if only one segment is affected
- Disease modifiers (e.g. fistulae, perianal disease) are unaccounted for
- Limited to the lower GI tract
- Scoring thresholds associated with specific prognostic values or endoscopic healing have not been validated
Summary

• Drug development is a lengthy process that requires the cooperation and collaboration amongst all stakeholders to be most successful.

• Clinical trials in IBD are moving towards co-primary endpoints that include both signs/symptoms and endoscopic findings.

• These co-primary endpoints in IBD are best measured by patient-reported and clinician-reported outcomes.

• Early and frequent interactions with FDA is encouraged to ensure successful planning and conduct of clinical trials.
Acknowledgements

• Jessica Lee, MD
References