Defining Clinical Benefit in Clinical Trials: FDA Perspective

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Disclosure Statement

- The views expressed in this talk represent my opinions and do not necessarily represent any official policies of the U.S. Food and Drug Administration.

- I have no financial interests to disclose.

Objectives

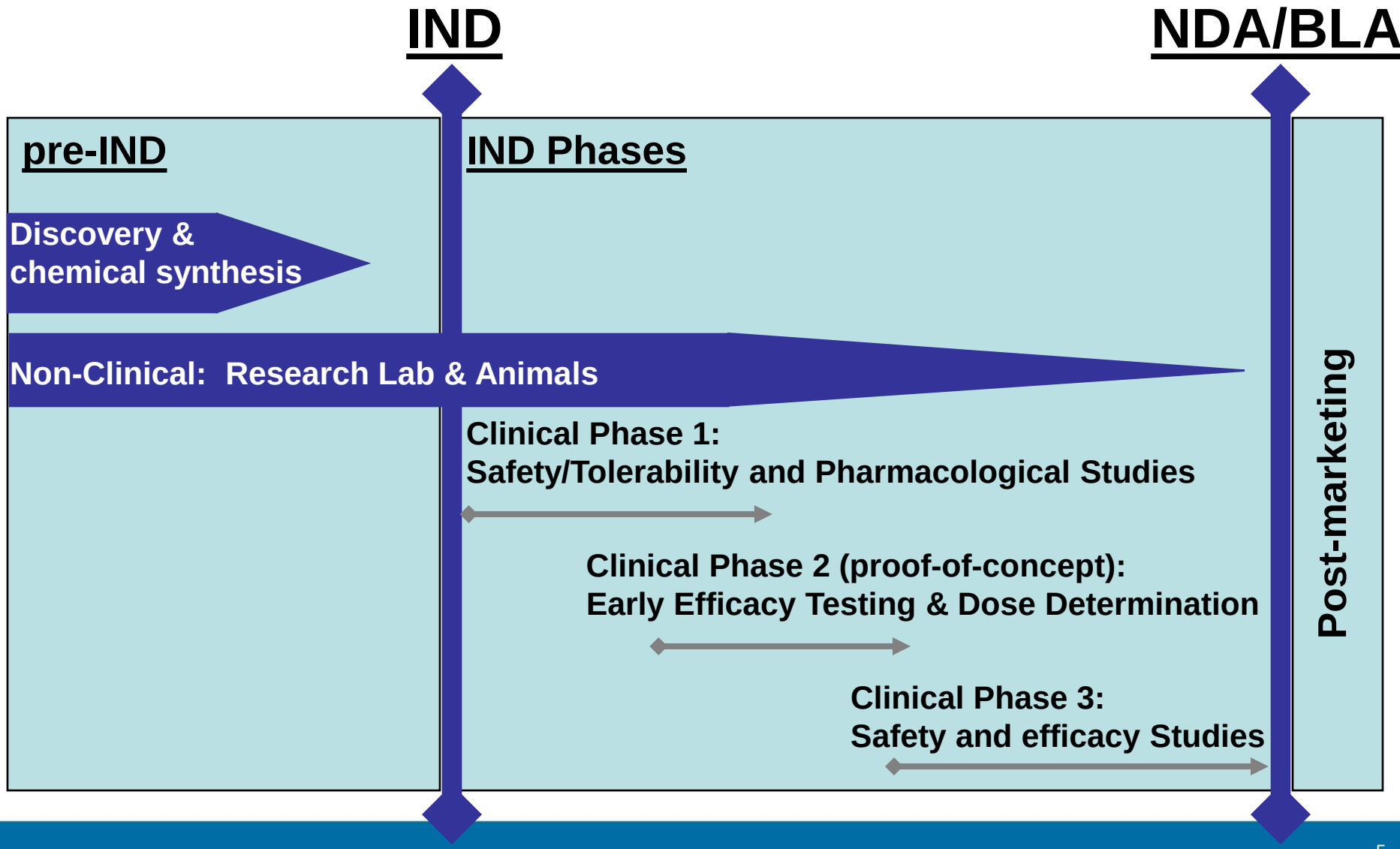
1. Basics of drug development process and FDA regulations

2. Defining clinical benefit from regulatory standpoint and considerations in celiac disease drug development

Drug Development Objective

- Provide evidence to establish that a drug is safe and effective for a specific indication.

New Drug Development Process



NDAs & BLAs

- **New Drug Applications (NDAs)**
  - 21 CFR 314
  - In general, small molecules

- **Biologics License Applications (BLAs)**
  - 21 CFR 600
  - Large proteins (e.g., enzymes, monoclonal antibodies) reviewed in CDER
  - Other biologics (e.g., vaccines, blood products, gene therapy products) reviewed in CBER

Level of Evidence of Efficacy: Legal Requirements

- 1962 Drug Amendments to the Food, Drug & Cosmetic Act:
  - Require establishment of effectiveness of the drug as a prerequisite for marketing approval
  - Effectiveness established by "**substantial evidence**"

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."

What are Adequate and Well-Controlled Studies?

- Studies that have been designed well enough 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 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

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).

Considerations when defining clinical benefit in celiac disease drug development

1. **Clarify the goal of the study drug**
   - Understand the mechanism of action of the drug
   - Adjunct therapy to a gluten-free diet *vs*. sole therapy?
   - Prevention of a flare *vs*. symptom treatment

2. **Identify the target population** (e.g., new diagnosis, non-responsive CeD, refractory CeD)
   - Should provide adequate assurance that enrolled patients have documented celiac disease and that their signs and symptoms are due to celiac disease
   - Should rule out other causes that mimic CeD

Considerations when defining clinical benefit in celiac disease drug development (cont'd)

3. **Identify signs/symptoms that would constitute a clinically meaningful benefit in the target population, if improved** (e.g., abdominal pain or diarrhea; histological improvement)
   - What are key signs and symptoms experienced by celiac disease patients whom you intend to treat with the drug?
   - In other words, improvement in what signs and symptoms will convince you that celiac patients have benefitted clinically after treatment?
   - Encourage patient involvement in the process

Considerations when defining clinical benefit in celiac disease drug development (cont'd)

4. **Select or develop clinical outcome assessment(s) (COAs) to assess clinical benefit** (e.g., patient-reported outcomes, histologic assessment)
   - How would you measure the key signs/symptoms experienced by celiac patients to demonstrate clinical benefit?
   - How would you ensure that the drug targeted signs/symptoms due to celiac disease and that underlying disease has not worsened despite symptom improvement?

Considerations when defining clinical benefit in celiac disease drug development (cont'd)

5. **Establish a responder definition using selected COA(s)**
   - What magnitude of change in score in the COA is considered clinically meaningful and will provide convincing evidence that the drug has shown clear benefit?

6. **Determine appropriate timing of efficacy assessment(s)**
   - Should be guided by the drug's mechanism of action and the type of endpoint being assessed

Conclusions

- Best access for patients to an effective therapy is an approved drug.
- To support marketing approval, treatments must demonstrate substantial evidence of effectiveness through adequate and well-controlled investigations.
- To design an adequate and well-controlled clinical trial requires well-described disease, acceptable endpoints, and tools/instruments to adequately assess the intervention.
- Clinical benefit is a favorable effect on a meaningful aspect of how a patient feels, functions, or survives as a result of treatment; described in labeling as a claim.
- Early planning in the drug development process is critical to meet challenges associated with defining appropriate efficacy endpoints and outcome measurement.

Thank you