U.S. FOOD & DRUG ADMINISTRATION

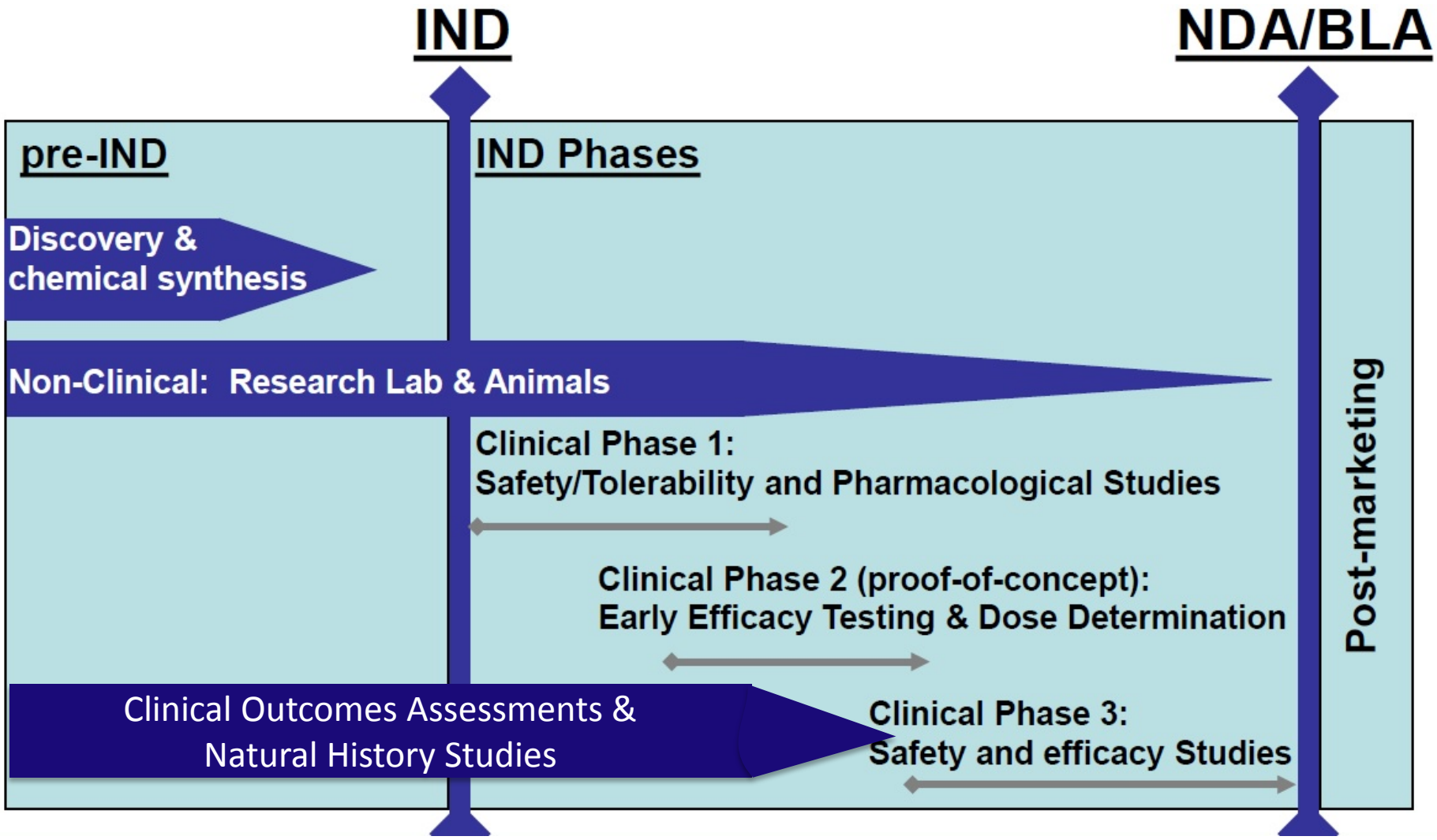
Understanding the Needs of CDER Drug Review Divisions

Elizabeth Hart, MD
Medical Officer
Division of Gastroenterology and Inborn Error Products
Office of New Drugs
Center for Drug Evaluation and Research
4/3/18

CDER Review Divisions

- **Evaluate efficacy and safety of new drug applications for specific indications by Sponsors**
- Agency involvement & advice often begins early during drug development
- Agency involvement continues post-marketing to further assess safety

New Drug Development



Level of Evidence of Efficacy: Legal Requirements

- 1962 Drug Amendments to the Food Drug & Cosmetic Act:
  - Required establishment of effectiveness of the drug as a prerequisite for marketing approval
  - Effectiveness established by **"Substantial Evidence"**
  - Substantial evidence consists of **"Adequate & Well Controlled Investigations"**

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:
  - **Appropriate control for valid comparisons**
  - Appropriate selection of subjects
  - **Well-defined and reliable methods of assessing response**
  - Adequate measure to minimize bias
  - Prospectively planned analyses designed with rigor

Defining Clinical Benefit

- Treatment benefit occurs when a drug positively effects
  - How a patient **feels** (e.g. symptoms)
  - How a patient **functions** (e.g. walks)
  - How a patient **survives** (e.g. improved mortality)
- Clinical effect must be clinically meaningful in the context of a given disease

Challenges in Drug Development for Rare Diseases

- Small population
  - Limited opportunity for study & replication
- Often Heterogeneous
  - Study population size limits statistical analysis
- Incomplete understanding of disease manifestations
- No precedent for drug development
  - Lack established endpoints, outcome measures & tools/instruments for the population

Drug Development:
(Especially for Rare Diseases)

Start with the end in mind: Obtain clinically meaningful evidence of benefit in how patients feel, function or survives from adequate and well controlled trial(s)

What Can Patient Organizations do to Facilitate Drug Development?

- Preform Natural History Study
- Provide Patient Experience Data
- Develop and Validate Qualitative and/or Quantitative Assessment Methods
- Encourage enrollment in randomized, controlled trials

Natural History Studies

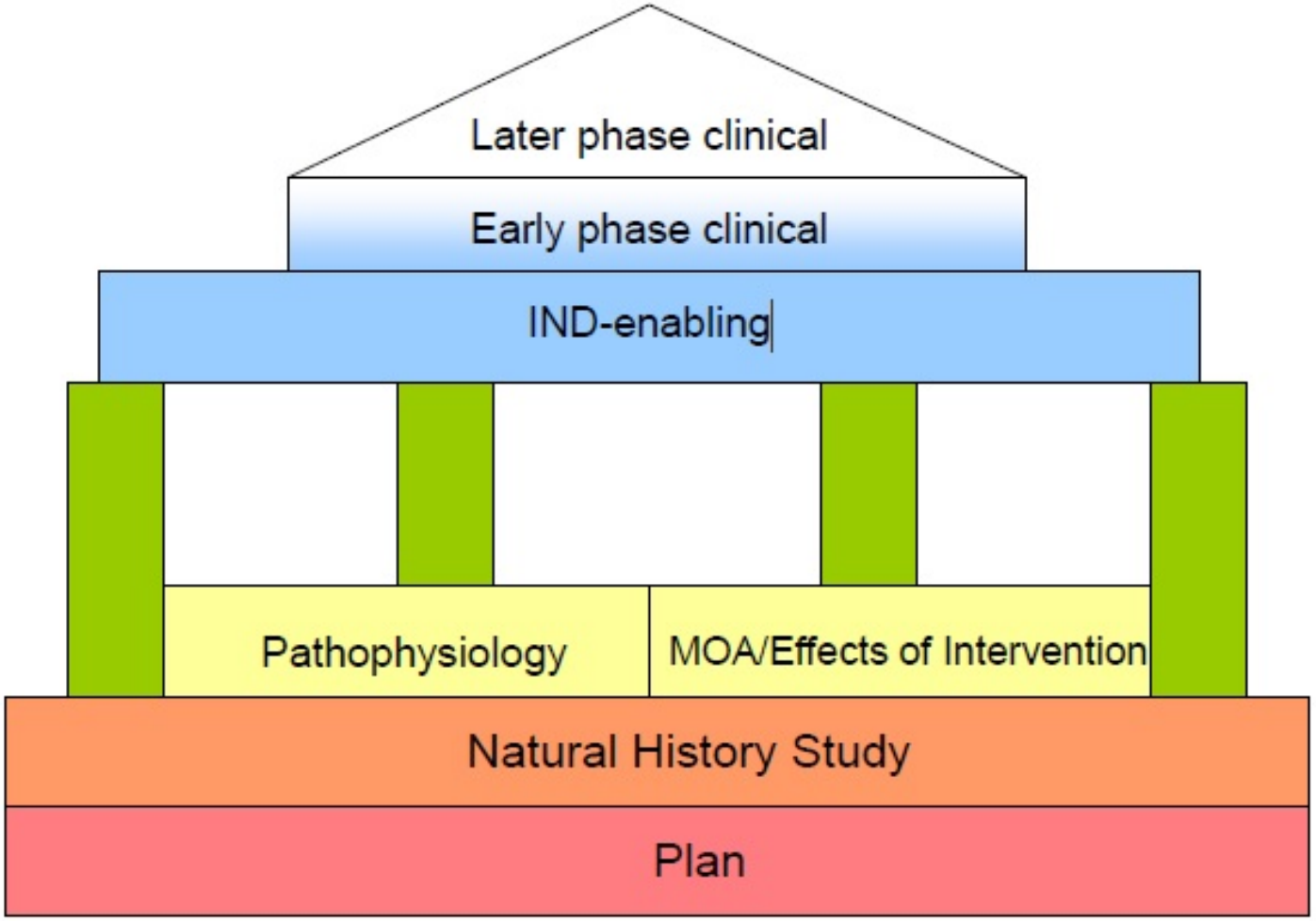
- Comprehensive study characterizing a disease or subset of disease over time
- Identify variables that correlate with disease progression and outcomes in the absence of experimental treatment
    - Demographic, genetic, environmental
- Cohort
    - Prospective or Retrospective
    - Include all stages of disease from pre-symptomatic to death/cure/non-progressive chronic disability

Why are Natural History Studies Important?

- Scientific framework for rigorous investigation
  - Understanding disease outcomes and variability
    - Endpoints
    - Population
    - Sample Size
- External control population for pivotal trial*
  - Reserved for special circumstances in which there is a dramatic treatment effect & disease course is highly predictable & endpoints are objective
    - Population & efficacy assessments comparable to interventional study populations

* FDA Guidance for Industry. E10 Choice of Control Group and related Issues in Clinical Trials. 2001.

Natural History Studies within the Regulatory Framework of Rare Disease Development



Patient Experience Data

- Inform Clinical Endpoints
  - Ensure bothersome signs and symptoms assessed
  - Ensure impact of condition on functioning and quality of life assessed

- Inform Benefit-Risk Assessment
  - Patient preference and tolerance for side effects

Assessment Tools

- Design and validate novel patient reported outcome measures
- Design and validate novel observer reported outcome measures
- Validate accuracy and reliability of tools originally developed for other disease populations

Clinical Trial Participation

- Patient participation is necessary for clinical trials & new drug development
  - Individual patients need to decide whether they are willing to undertake the burdens and potential risks associated with clinical trial participation
- Randomized, placebo/standard of care, controlled clinical trials are the most informative as they control bias

Conclusions

- Best access for patients to an effective therapy is an approved drug.
- Patient engagement early & throughout development process is important to informing drug development and regulatory decision making.
- You can help the FDA by early engagement and use of scientifically sound methods to collect representative patient data for natural history studies and endpoint selection and measurement.


FDA
U.S. FOOD & DRUG
ADMINISTRATION