Select Challenges in IBS Clinical Trials:

Regulatory Perspective

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Disclosures

- I have no financial interests to disclose

- The views expressed in this talk represent my opinions and do not necessarily represent any official policies of the FDA or DGIEP

Overview

- Basic Regulations for Drug Approval
- Select challenges in IBS trials intended to support drug approval
- FDA Guidance for Industry: Irritable Bowel Syndrome (IBS)

Statutory Requirements for New Drug Approval

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

- For the proposed patient population, the benefits of the drug outweigh its potential risks
- Manufacturing that ensures product identity, strength, and quality
- Evidence-based drug labeling that adequately guides providers and patients to use the drug safely and effectively

Amendments to the Food, Drug, and Cosmetic Act, 1962

Regulatory Requirements: Demonstrating Efficacy

1962 Drug Amendments to the Food, Drug & Cosmetic Act:

- Requires the establishment of drug effectiveness as a prerequisite for marketing approval
- Effectiveness is demonstrated by **"substantial evidence"**

21CFR 314.50 and 21CFR 314.126

Benefit of Therapy

- A favorable effect on a meaningful aspect of how a patient ***feels, functions, or survives*** as a result of treatment*
- Clinically meaningful, measurable, and interpretable
- Labeling claim(s) using words that represent the measured concept

**Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims; FDA PRO Guidance*

IBS: "Functional Gastrointestinal Disorder"

- Describes a spectrum of chronic GI conditions
  - Chronic time course and unpredictable symptom exacerbations
- There are no known anatomical, structural, or biochemical abnormalities
- Signs and symptoms are believed to be related to abnormal intestinal motility, abnormal intestinal perception, and/or abnormal brain-gut communication
- Diagnosis: signs and symptoms ascertained from the patient
  - The Rome Diagnostic Criteria

Rome IV Diagnostic Criteria

IBS is defined as recurrent abdominal pain, on average, at *least 1 day per week* in the last 3 months

- associated with 2 or more of the following criteria:

- Related to defecation
- Associated with a change in stool frequency
- Associated with a change in stool form

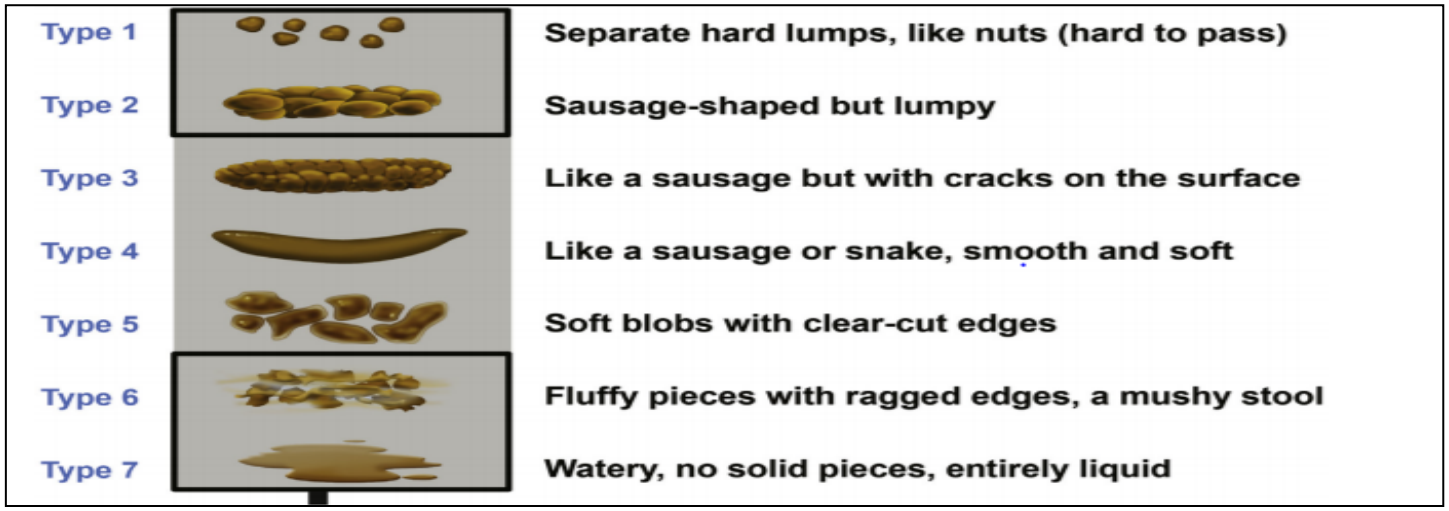


Image from Lacy BE, Mearin F, Chang L, et al. Bowel disorders. Gastroenterology 2016; 150:1393

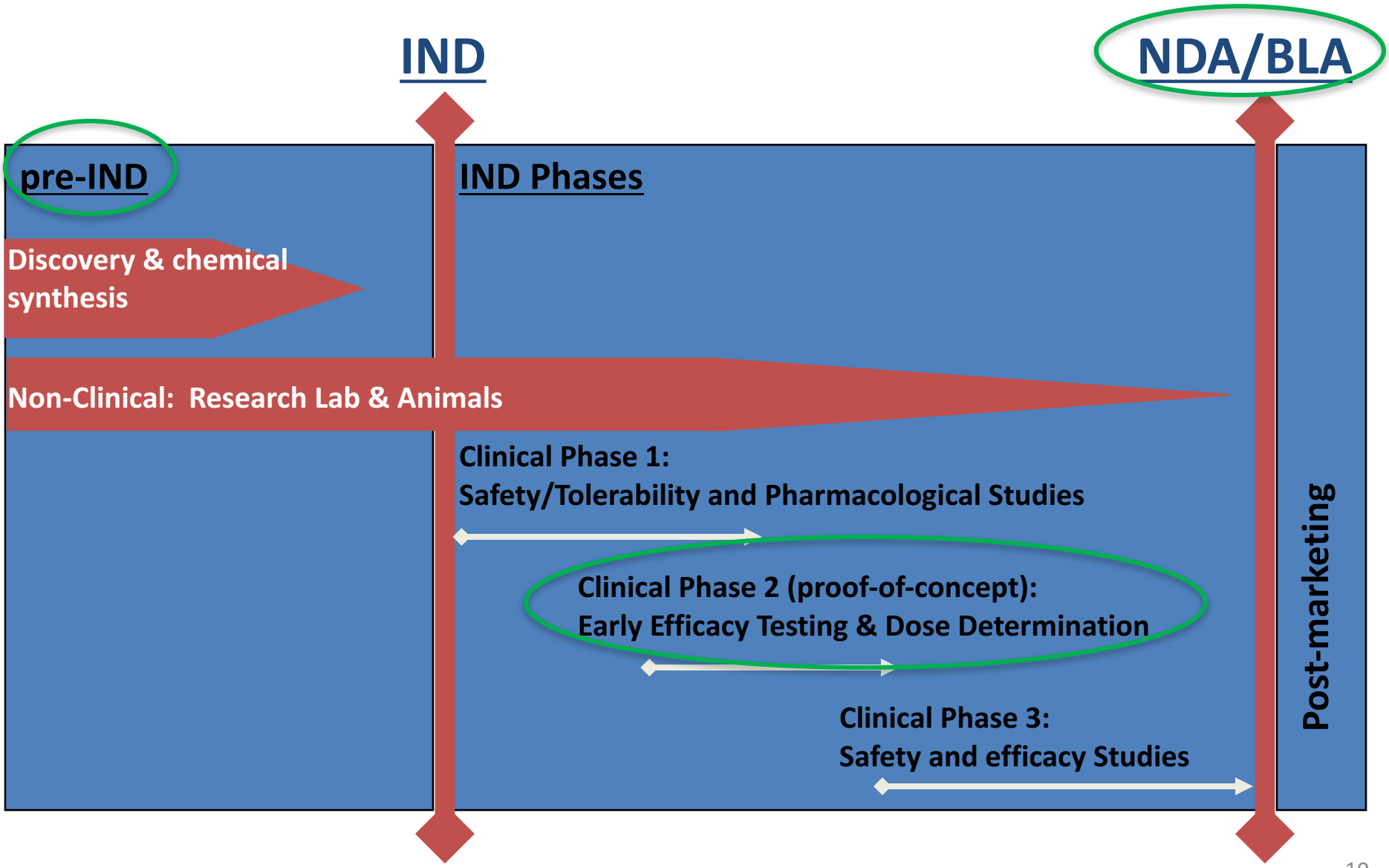
Collaborating in IBS Drug Development

- We work with multiple stakeholders, including patients, pharmaceutical companies, academia, and professional societies
- The patient perspective is key

Voice of *the Patient*

- Public meeting on Functional GI Disorders Patient-Focused Drug Development

Drug Development Process for IBS



Select Challenges

in IBS Drug Development

The Importance of Patient-Reported Outcomes

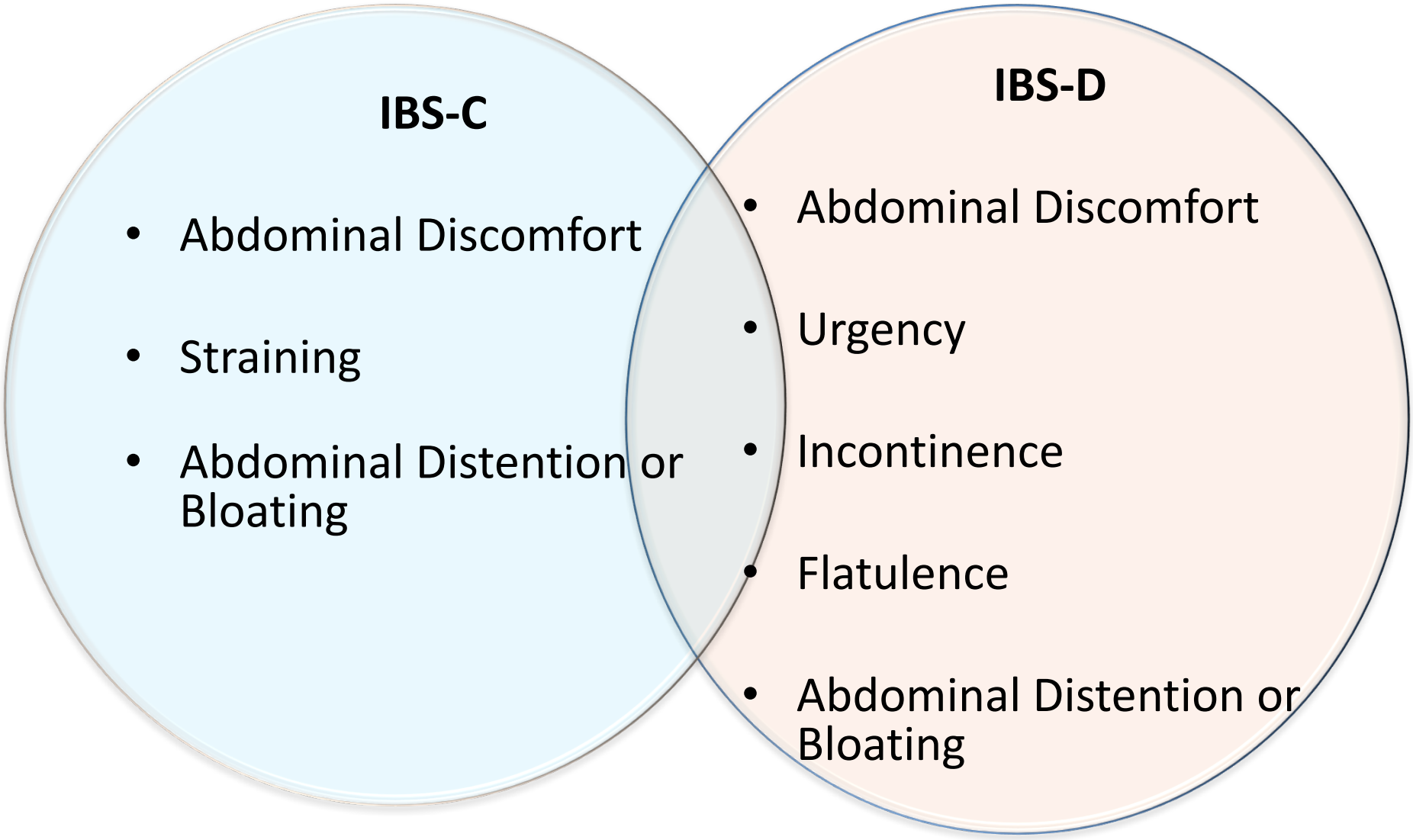
- Patient-reported outcomes (PROs) can represent direct measures of treatment benefit regarding how a patient feels or functions

- Patient input is essential to capture important and clinically-relevant disease signs and symptoms

Differentiating Abdominal *Pain* and Related Symptoms

- Are abdominal *pain* and abdominal *discomfort* describing the same symptom?
- Abdominal *distension* or *bloating*
  - Are they redundant with pain or discomfort?

Additional IBS Symptoms and Signs



Additional Select Challenges

- Benefit vs. Risk of Therapy
- Explore doses and efficacy endpoint(s)
- Assess *within* patient changes and responder definitions
- Trial design and placebo response rate
- Trial duration and treatment durability

Guidance for Industry

Irritable Bowel Syndrome — Clinical Evaluation of Drugs for Treatment

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 51, rm. 2201
Silver Spring, MD 20993-0002
Tel: 301-796-3400; Fax: 301-847-8714; E-mail: druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

May 2012
Clinical/Medical

IBS Guidance Recommended Primary Endpoints Components

Abdominal Pain Intensity

- and-

Abnormal Defecation

IBS-C: stool *frequency*

IBS-D: stool *consistency*

Abdominal Pain Intensity: Responder Definition

- An *Abdominal Pain Intensity Responder* is defined as a patient who experiences a decrease in the worst abdominal pain of **at least 30 %** compared with baseline (in the past 24 hours)

- *Overall responder:* patient achieves the pre-specified improvement in weekly or daily response for at least half of the weeks or days of treatment

IBS Guidance
Recommended Trial Entry Criteria

FDA

IBS-C (constipation)

- **Abdominal Pain Intensity:** weekly average of *worst daily (in past 24 hours) abdominal pain* score of ≥3.0 on a 0 to 10 point scale

and

- **Stool Frequency:** fewer than 3 CSBMs (complete spontaneous bowel movements) per week

IBS-D (diarrhea)

- **Abdominal Pain Intensity:** weekly average of *worst daily (in past 24 hours) abdominal pain* score of ≥3.0 on a 0 to 10 point scale

and

- **Stool Consistency:** at least 1 stool with a consistency of Type 6 or Type 7 Bristol stool score (BSS) on at least 2 days per week

Final Thoughts

- Many challenges in the clinical development of IBS therapies
- Encourage early collaboration
- Consider leveraging phase 2 trials to optimize program success by:
  - Define Endpoints
  - Define clinically meaningful effect size
  - Identify appropriate doses for phase 3 trials
  - Consider the placebo response rate in IBS trials

Thank you and Acknowledgements

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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.
- US Food and Drug Administration. Guidance for Industry: Irritable Bowel Syndrome – Clinical Evaluation of Drugs for Treatment. May 2012. https://www.fda.gov/ucm/groups/fdagov-public/documents/document/ucm205269.pdf

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- Irvine EJ, Tack J, Crowell MD, Gwee KA, Ke M, Schmulson MJ, Whitehead WE, Spiegel B. Design of Treatment Trials for Functional Gastrointestinal Disorders. Gastroenterology. 2016 May;150(6):1469-1480.e1. doi: 10.1053/j.gastro.2016.02.010.
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