Supporting the First Harmonized Bioequivalence Guideline Under ICH:
Considerations for Future Implementation

SBIA 2023—Advancing Generic Drug Development: Translating Science to Approval

Day 2, Session VIII: Global Collaboration to Support Efficient Generic Product Development & Regulatory Assessment

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September 14, 2023

Learning Objectives

- Provide an overview of ICH M13 guideline series and progress to-date

- Discuss the next steps by the ICH M13A Expert Working Group (EWG)

- Discuss strategic planning for future implementation of ICH M13A by FDA
  - FDA research supporting ICH M13A

ICH: The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; ICH M13A: Bioequivalence for Immediate-Release Solid Oral Dosage Forms

M13 Guideline Series

BE: Bioequivalence; HVD: highly variable drug; NTI: narrow therapeutic index

Progress Status of M13

M13A

- **Current Status:** Step 3 Regulatory consultation and discussion

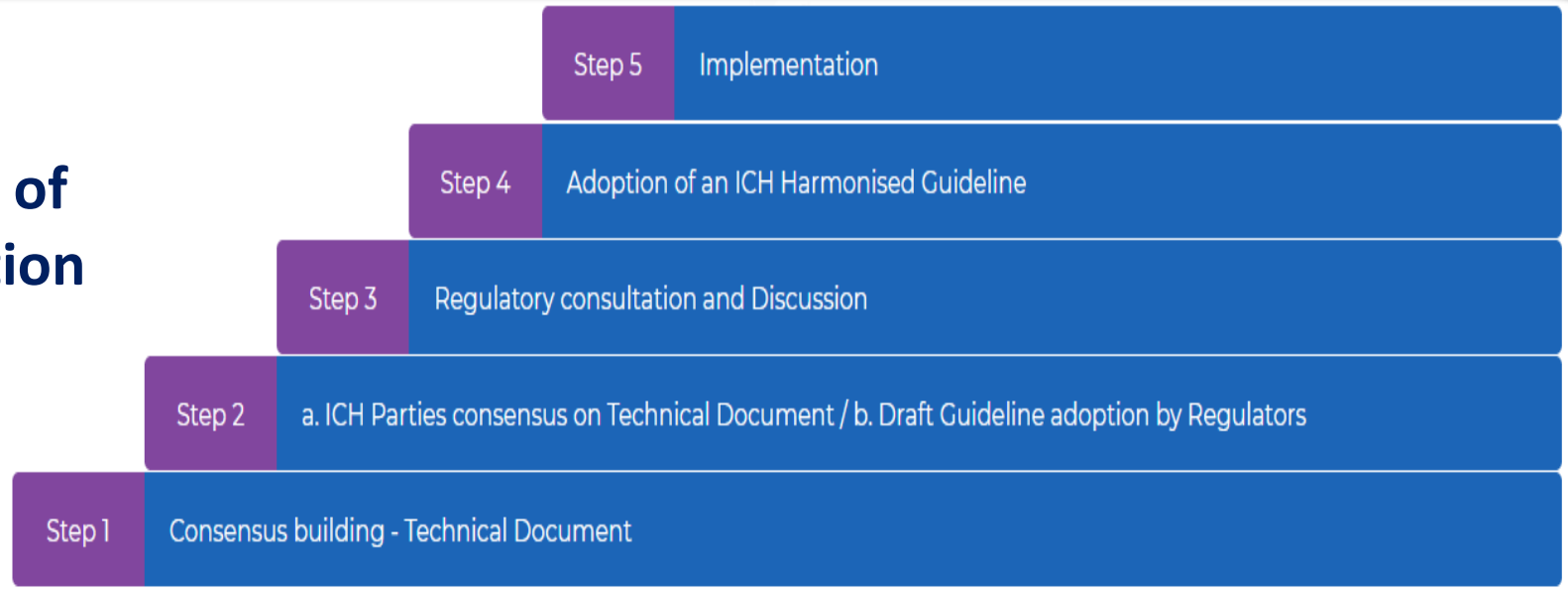
M13B

- **Current Status:** Step 1 Draft technical document under development towards consensus

M13C

- Start: After M13B *Step 2*

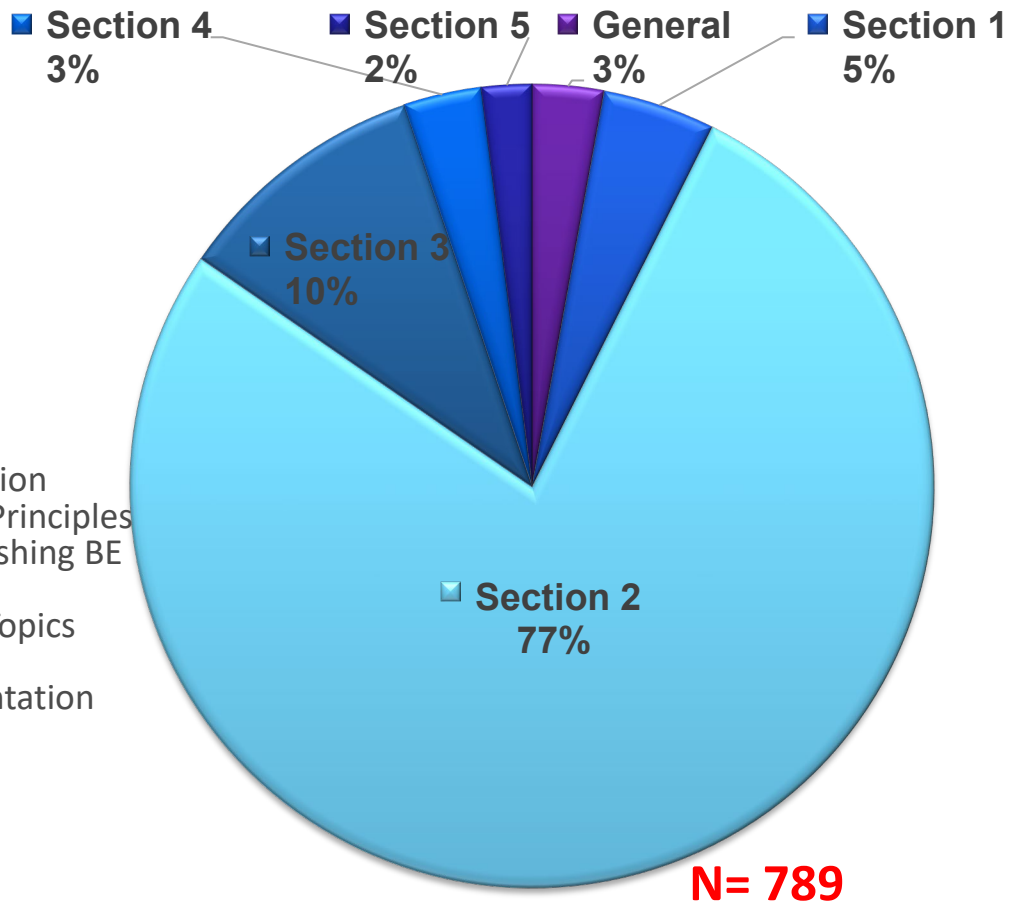
ICH Process of Harmonization



Working towards Adoption of M13A (Step 4)

Continuing Efforts by M13A EWG

1. EWG members will address the comments through consensus and revise the guideline to support finalization



1. Introduction
2. General Principles in Establishing BE **(77%)**
3. Specific Topics **(10%)**
4. Documentation
5. Glossary

2. Develop Q&A document to provide details and clarification for the scientific thinking for some recommendations

3. Develop training materials to facilitate regional implementation and ensure consistency

"…the proposed guidance is excellent. It is clearly written, scientifically sound, and overall an important step towards promoting harmonisation of global drug development"

Strategic Planning for Future Implementation of M13A

Tasks Anticipated by FDA for M13A Implementation

- Developing FDA training materials
    - internal and external stakeholders
- Updating the current PSGs to align with the recommendations in M13A
- Updating the FDA's draft guidance on *BE studies with PK Endpoints for Drugs Submitted under an ANDA*
    - currently the guidance includes recommendations for both immediate-release and modified-release products
- Assessing the need to update the BE summary tables
- Continuing research on select topics

PSG: Product-Specific Guidance; PK: pharmacokinetic; ANDA: Abbreviated New Drug Application

FDA Research on Select Topics

1. Fasting and Fed BE

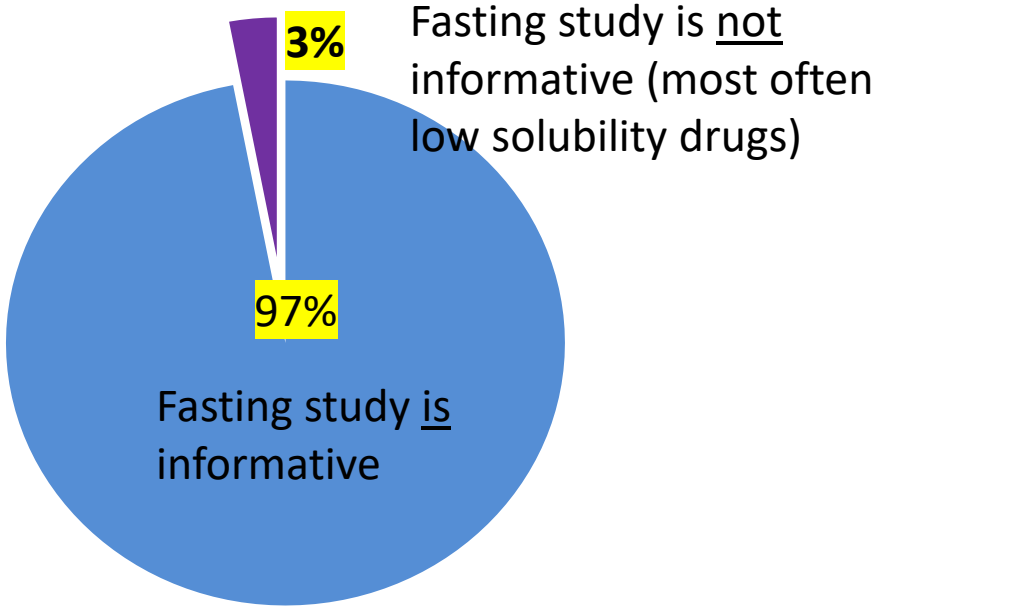
- Food can have a differential, formulation-dependent impact on the absorption of drug substances from drug products in some cases

- Applicants should have a thorough understanding of comparator and test formulations to determine if BE under both fasting and fed is warranted

- Rationale for selection of the study design with regard to the use of fasting and/or fed conditions may be supported by,
  - modelling, e.g., appropriately validated/qualified physiologically based pharmacokinetic (PBPK) modelling or semi-mechanistic absorption models

Evaluating the Need for Fed Studies

Survey of IR Products by Generic Industry* (2019)



* https://www.fda.gov/media/125172/download

FDA's Retrospective Analysis of Data for High Solubility IR Products

Food-excipient interactions

- In some cases, excipients such as swellable disintegrants or fillers affected the rate of absorption of highly soluble drugs differently in the fed state

Extramural Research Related to Fed BE Studies

1. "Model-informed biowaivers of fed BE studies for BCS Class II drugs" (Grant: 1U01 FD007352-01)
   - Develop an oral PBPK model
     - consider the possible impact of formulation variables in the model to assess the impact under fed conditions
   - Simulate the results of BE studies to predict the impact of food on oral drug absorption for certain poorly soluble drugs

2. "Develop an evaluation algorithm to determine if a fed BE study can be waived based on disintegration and dissolution methodologies that mimic food induced viscosity" (Contract: 75F40121C00020)
   - Some excipients are known to influence the disintegration and dissolution of drug products differently under enhanced viscosity

https://www.fda.gov/media/154295/download?attachment

Extramural Research, continued

Results from these research projects will be presented at the public workshop on October 12, 2023

FDA-CRCG Workshop: Advances in PBPK Modeling and its Regulatory Utility for Oral Drug Product Development (complexgenerics.org)

CRCG: Center for Research on Complex Generics

FDA Internal Research

1. “Evaluating the application of Bayesian Dynamic Borrowing Approaches in the fed PK BE studies by borrowing the BE results from the fasting PK studies as ‘informative prior’
2. “Investigating the impact of food-induced fluid viscosity increase on disintegration and dissolution of solid oral IR products”
3. “Using PBPK absorption modeling to evaluate the impact of food on bioequivalence”

pH-Dependency

- Newly introduced general recommendation for an additional BE study* with concomitant treatment of a pH-modifying drug product (e.g., PPIs) for drugs showing pH-dependent solubility and dissolution
  - lack of sufficient knowledge/experience of almost all regulators, in this topic area

- Can justify not conducting an in vivo study by assessing the bioinequivalence risk, based on totality of evidence
  - pH-solubility profile, impact of excipients, formulation and manufacturing design (e.g., formulation designed to overcome pH effects), comparative dissolution testing at multiple pHs, modelling, etc.

* FDA recommends an additional fasting BE study in presence of acid-reducing agent in the PSG for Palbociclib Tablets

Research to Facilitate Implementation pH-Dependency

1. Expand the extramural research project on oral PBPK modeling framework to hypochlorhydria populations

2. FDA internal research

   Using Modeling and Simulations to Support Bioequivalence (BE) Study Design and Evaluate the Impact of Gastric pH on BE

   - Performing virtual bioequivalence simulations

Key Takeaways

- The draft M13A is an ICH guideline under finalization (in Step 3) and will not be implemented until the guideline is finalized and adopted by FDA (in Step 5)
- FDA has initiated research to facilitate the implementation of some key recommendations that present a major change from FDA's current practice
- FDA intends to update the relevant guidance documents to align with the recommendations in M13A when it is finalized
- FDA's current practice and draft M13A offer flexibility. Prospective applicants may provide appropriate scientific justification, if they propose an alternate approach and deviate from the guidance recommendations

Polling Question # 1

FDA will implement the draft ICH M13A guideline

True

False

Polling Question # 2

The ICH M13 guideline is being developed in 3 series

True

False