ICH M13A: First ICH Guideline for Bioequivalence

Advancing Generic Drug Development 2024: Translating Science to Approval

Day 2, Session 6: Ensuring Efficient and Consistent High Quality Generic Drug Development

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September 25, 2024

Learning Objectives

- Provide an overview of the M13 guideline series
- Provide an overview of the final M13A guideline and major changes from the draft guideline
- Provide an update on the FDA planning on the implementation of M13A for generic drug applications

Bioequivalence Assessment

Bioequivalence (BE) assessment is important for establishing therapeutic equivalence for generic drug products to their respective reference listed drugs (“comparator” products)

- BE ensures that generic drugs demonstrate comparable pharmacokinetic properties to their brand-name counterparts
- There may be situations in new (innovator) drug development when demonstration of BE may be critical for approval decisions
- BE studies are used by innovator and generic product developers for supporting post-approval formulation and/or manufacturing process changes

*__Comparator__ is defined in M13A as “an investigational or marketed product, i.e., active control, or placebo, used as a reference in a clinical trial. In the context of this guideline, a comparator product is the drug product accepted by regulatory agencies that an applicant can use to compare against the test product in conducting a BE study."

M13 Guideline Series

M13A

BE for immediate-release solid oral dosage form (BE study design and analysis)

Current Status:

Step 5 Implementation

M13B

BE for additional strength including additional strength bio-waiver

Current Status:

Step 1 Draft technical document under development towards consensus

M13C

Data analysis and BE for:

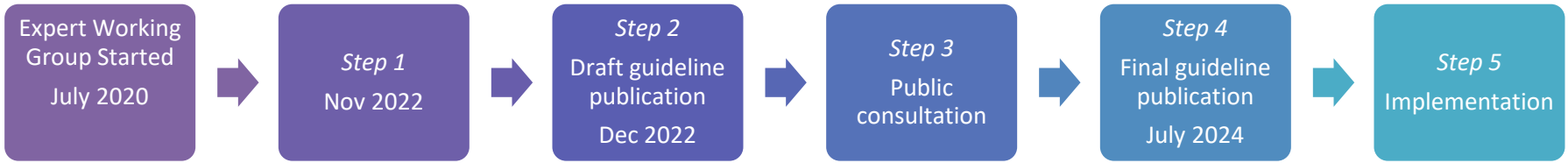
1. Highly variable drugs
2. Narrow therapeutic index drugs
3. Complex study design and data analysis (e.g., adaptive design)

Current Status:

Will start after M13B reaches *Step 2*

BE: Bioequivalence

M13A Timeline



ICH Process of Harmonization

www.ich.org

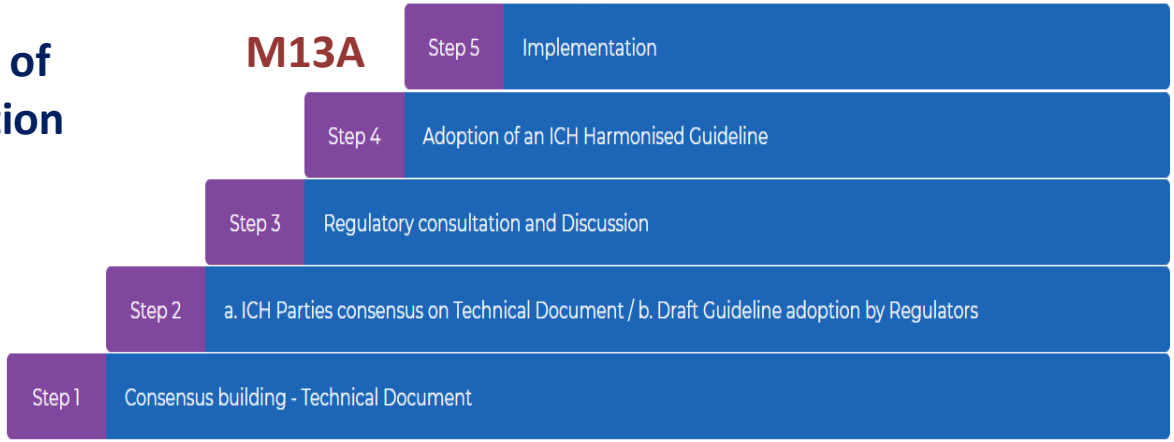


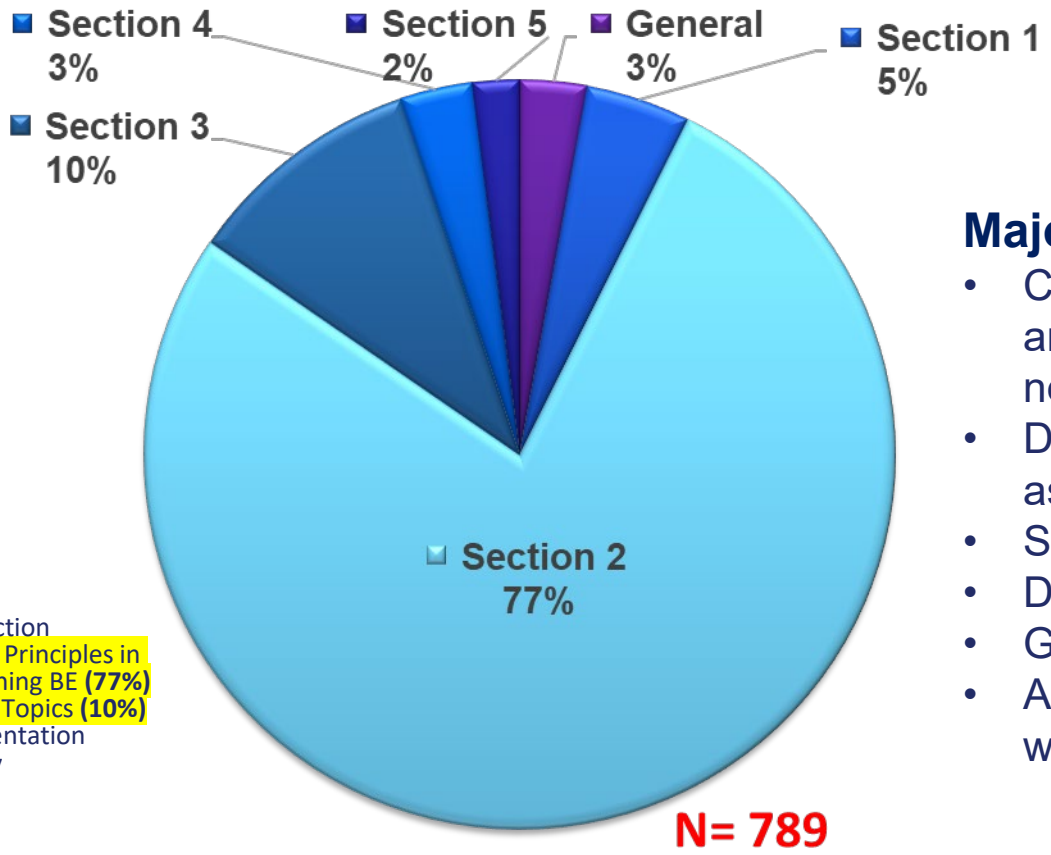
Table of Contents of M13A Guideline (1)

- **1. Introduction**
  - 1.1 Objective
  - 1.2 Background
  - 1.3 Scope
- **2. General Principles in Establishing Bioequivalence**
  - 2.1 Study Design for Pharmacokinetic Endpoint Bioequivalence Studies
  - 2.2 Data Analysis for Non-Replicate Study Design

Table of Contents of M13A Guideline (2)

- **3. Specific Topics**
  - 3.1 Endogenous Compounds
  - 3.2 Other Immediate-Release Dosage Forms
  - 3.3 Fixed Dose Combination
  - 3.4 pH-Dependency
- **4. Documentation**
- **5. Glossary**

Comments Received



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

Major Comment Themes

- Clarification on “high risk” and when fed BE study is needed
- Dose proportionality assessment
- Study population
- Data analysis
- Group effect
- Alignment of study design with product labeling

Main Changes Made from the Draft Guideline

- Modifications are made based on comments received
- Mainly to provide clarification, e.g.,
  - "High risk" products
    - "…drug products with special characteristics that result in a higher risk of **bioinequivalence** due to food effects…"
  - Data analysis
  - PK dose proportionality assessment
  - Early exposure
  - pH-dependency

Additional Resources Provided

- "Questions and Answers" document
  - To provide further clarity and to assist implementation
    - Section 2: 11 Q&A
    - Section 3: 7 Q&A
    - Section 4: 1 Q&A
- Step 4 Presentation

ICH M13A Questions and Answers (July 2024)
ICH M13A Step 4 Presentation (July 2024)

Before M13A

- Different regulatory agencies have different recommendations for BE study designs and criteria to support generic drug approval
  - For immediate-release (IR) oral products
    - FDA generally recommended both fasting and fed BE studies
    - Several other regulatory agencies including European Medicines Agency (EMA), generally recommended a BE study under fasting conditions only
- Differences in general BE guidances led to different product-specific guidance (PSG) recommendations

Before M13A: Different PSG Recommendations Between FDA and EMA for IR Solid Oral Drug Products

	U.S. FDA	EMA
General guidance regarding PK BE study fasting/fed recommendations	FDA generally recommends both a fasting and fed BE study	Conducted under fasting conditions; Fed BE study is recommended based on labeling recommendations or specific formulation characteristics
General guidance regarding PK BE study subject selection	Generally performed in healthy subjects, unless the drug carries safety concerns that make this approach unethical	
PSGs published as of 12/31/2022	1051	63
PSGs recommending in vivo PK endpoint studies	88%	100%
PSGs recommending both fasting/fed BE studies	86.6%	15.9%
PSGs recommending fasting BE study only	9.2%	69.8%
PSGs recommending fed BE study only	1.2%	14.3%
PSGs recommending healthy subjects	94.3%	92.1%
PSGs recommending patient subjects	5.5%	7.9%

**Published PSGs for IR solid oral products were obtained through the FDA's PSG database (September 2008–December 2022)*

**Kotsybar J, et. al., Global harmonization of immediate-release solid oral drug product bioequivalence recommendations and the impact on generic drug development, Clinical and Translational Science, Oct 2023 (https://doi.org/10.1111/cts.13670)

M13A: High-Risk and Non-High-Risk Products

- **High-Risk Products (Risk of BE Failure)**
  - For certain products, differences in formulation and/or manufacturing process may not be detected with a single BE study, i.e., results from a fasting BE study may not be extrapolated to predict fed BE study outcome or vice versa
  - BE studies should be conducted under both fasting and fed conditions (Q&A 2.4 and Q&A 2.5)

- **Non-High-Risk Products**
  - Results from a fasting BE study may be extrapolated to predict fed BE study outcome or vice versa
  - BE testing under only one condition, generally fasting, is sufficient

High-Risk Products

(Risk of BE Failure)

Includes drug products containing low solubility drug substances that are formulated using,

- specialized technologies and/or manufacturing methods to optimise the food effect or enhance the solubility and dissolution. E.g.,
  - microemulsions
  - amorphous solid dispersions
  - lipid-based formulations
  - nanotechnology
- substantially different manufacturing technology or particle size control method for the test and comparator products

  or
- have excipient differences that are likely to impact dissolution, solubility, or permeability of the test and comparator products differently

Meal Type for Fed BE Study

- **High-Risk Products**
  - Fed BE: irrespective of the product labeling with regard to food intake
    - The meal should be a high-fat and high-calorie meal*
- **Non-High-Risk Products**
  - Fed BE: e.g., where the labeling indicates intake only under fed conditions, due to a PK reason
    - Either a high-fat, high-calorie meal or a low-fat, low-calorie meal, may be administered (Q&A 2.6)
    - Labeling specified meal

** For BE studies in patients, a different fat/calorie content meal may be used as appropriate for the patient population.*

Fasting and Fed BE

Current FDA Draft ANDA BE Guidance:

Recommends Both Fasting and Fed BE Studies for All Oral IR Drug Products	
Fasting BE Studies Only	1) Products should be taken on an empty stomach (per the labeling) 2) Serious adverse events are anticipated under fed conditions
Fed BE Studies Only	1) Serious adverse events are anticipated under fasting conditions

ICH M13A:

Depending on the dosing instructions of the comparator product as well as the properties of the drug substance and product formulation	
Fasting BE only*	1) Non-high-risk products 2) Serious adverse events are anticipated under fed conditions
Fasting and Fed BE	High-risk products**
Fed BE only	1) Non-high-risk products, labeled to be taken with food due to PK reasons 2) Serious adverse events are anticipated under fasting conditions

* Fasting or fed BE: where the labeling indicates intake only under fed conditions, due to tolerability reasons

** Irrespective of the product labelling with regard to food intake, except for safety concerns

FDA Draft Guidance: Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application (August 2021)

ICH M13A Final Guideline (July 2024)

FDA Harmonization and Alignment Efforts

- FDA is leading the harmonization efforts at ICH
- FDA will revise majority of immediate-release (IR) product PSGs to align with M13A following a risk-based approach
  - BCS classes, formulation design (critical excipients), food effect, labeling, etc.
  - ~800 PSGs (recommending BE to be conducted in healthy subjects)
    - Two BE studies → One BE study (either under fasting or fed conditions)
- Aim to publish the revised PSGs in 4Q 2024

https://www.fda.gov/drugs/guidances-drugs/product-specific-guidances-generic-drug-development

Significance of M13A

- First harmonized ICH guideline that focuses on BE
- Impacts a significant portion of the pharmaceutical market
  - IR products account for ~46% of approved new drugs in the U.S.
- Reduces the need for additional in vivo BE studies due to divergent regulatory recommendations prior to harmonization
  - "Risk-based" approach to determine BE study with regard to meals (fasting vs. fed vs. both)
    - Major area of divergence prior to harmonization
- Supports streamlined global drug development
  - Study design with multiple arms to include multiple comparators or multiple test products
- Benefits patients by increasing access to generic drugs

Key Takeaways

- ICH M13A has been finalized, adopted by ICH, and is ready for implementation by ICH regulatory members including FDA and other global regulatory agencies (in *Step 5*)
  - Facilitate regulatory approval
  - Promote confidence in generic drugs
  - Enhance global access to affordable medicines
- FDA is updating the relevant guidance documents to align with the recommendations in ICH M13A
  - General BE guidance and product-specific guidances for ANDAs
- FDA's current practice and ICH M13A offer flexibility. Prospective ANDA applicants may provide appropriate scientific justification, if they propose an alternate approach and deviate from the guidance recommendations

ANDA: abbreviated new drug application

Save the Date

- SBIA Webinar on ICH M13A final guidance
  - Nov 21, 2024, 1-3 PM

Challenge Question 1

- Following the implementation of ICH M13A guidance, which of the following will represent the most significant changes in FDA's recommendations for BE studies for immediate-release solid oral drug products?

  A. BE study design with regard to food conditions
  B. BE study population
  C. BE for long half-life drugs
  D. Batch size for pivotal BE studies

Challenge Question 2

- FDA will revise product-specific guidances for immediate-release oral drug products to align with ICH M13A

  A. True

  B. False

Resources

- ICH M13A Final Guideline (July 2024)
- ICH M13A Questions and Answers (July 2024)
- ICH M13A Step 4 Presentation (July 2024)
- FDA Draft Guidance: Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application (August 2021)
- FDA Draft Guidance: Statistical Approaches to Establishing Bioequivalence (December 2022)
- FDA Office of Generic Drugs Global Generic Drug Affairs
- Product-Specific Guidances for Generic Drug Development (main page)