

ICH M13: Bioequivalence for Immediate-Release Solid Oral Dosage Forms

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John Gordon, Ph.D.
Bureau of Pharmaceutical Sciences
Pharmaceutical Drugs Directorate
Health Canada



Presentation Outline

- Objectives / Scope / Organisation for M13
- Current status
- Organisation of M13A document
- Highlights of M13A document
- Conclusions / Next Steps

Objective of M13

- To provide recommendations on conducting bioequivalence (BE) studies during:
 - Product development
 - Post-approval phases
- Immediate-release (IR) solid oral dosage forms designed to deliver drugs to the systemic circulation. For example,
 - Tablets
 - Capsules
 - Granules/powders for oral suspension

Objective of M13

- Harmonisation of current regional guidelines/guidances
- Reduce need to conduct multiple BE studies for multiple jurisdictions
 - Reduce the need for additional in vivo BE studies
- Support streamlined global drug development

Scope and Organisation of M13

- M13 process includes three (3) tiers
- M13A; First guideline in the series
 - Scientific / technical aspects of study design and data analysis to support BE assessment
 - How regulatory decisions are made based on the BE assessment is out of scope
 - Acceptance of comparator products across regulatory jurisdictions
 - Could reduce burden of multiple clinical trials
 - Governed by local laws therefore out of scope

Scope and Organisation of M13

- M13B; Second guideline in the series
 - Requirements for additional strengths of a product line
 - BE study(ies) conducted with one (reference) strength
 - Relationship to reference strength
 - Biowaiver from requirement for additional studies
- M13C; Third guideline in the series
 - BE study design, analysis, and assessment for
 - Highly variable drugs
 - Drugs with narrow therapeutic index (NTI)
 - Complex study design and analysis considerations

Current Status

- M13A
 - Endorsed by ICH 20 December 2022 (Step 2b)
 - Currently being posted by ICH Regulatory Members for public consultation (Step 3)
 - FDA deadline for comments – 3 April 2023
 - Health Canada deadline for comments – late May 2023
- M13B
 - Consensus building leading to development of draft document began in November 2022
- M13C - pending

Organisation of M13A Guideline

- 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

Organisation of M13A Guideline

- 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

Study Design

- Study Population
 - Normally healthy subjects
- Study design
 - Normally a randomised, single-dose, two-period, two-sequence crossover study design
 - For safety/tolerability reasons, possibly single-dose or multiple-dose study in patients
 - For drugs with a long elimination half-life: parallel design
- Sample size calculation

Study Design

- Test Product
 - Representative of product to be marketed
- Comparator Product
 - Product accepted by regulatory authorities that can be compared against the Test Product in BE study
- Strength to be studied
 - Dependent on the pharmacokinetics of the drug

Study Design – fasting and/or fed conditions

- Selection of the type of BE study(ies) (fasting or fed or both) and meal type(s) depends on
 - The dosing instructions of the comparator product
 - The properties of drug substance
 - The properties of the products being compared (non-high-risk or high-risk)

Study Design – fasting and/or fed conditions

- **High-risk products**

- Products where the complexity of the formulation design or manufacturing process leads to an increased likelihood that in vivo performance will be impacted differently by varying gastrointestinal (GI) conditions between the fasted and fed states
- Example of such products: solid dispersions, microemulsions, lipid-based formulations, nanotechnologies, or other specialised technologies

Study Design – fasting and/or fed conditions

- Non-high-risk products:
 - Fasting: where the labelling indicates intake only under fasting or under fasting or fed conditions
 - Fed: where the labelling indicates intake only under fed conditions, due to a pharmacokinetic (PK) reason
 - Fasting or fed: where the labelling indicates intake only under fed conditions, due to tolerability reasons

Study Design – fasting and/or fed conditions

- High-risk products:
 - BE studies should be conducted under both fasting and fed conditions

Data Analysis

- The following single-dose PK parameters should be tabulated:
 - Primary parameters: $AUC_{(0-t)}$ (or $AUC_{(0-72h)}$), C_{max}
 - Additional parameters: $AUC_{(0-inf)}$, $AUC_{(0-t)}/AUC_{(0-inf)}$, T_{max} , k_{el} , $t_{1/2}$
 - $AUC_{(0-t)}$ should cover at least 80% of $AUC_{(0-inf)}$, except in case AUC is measured over 72 hours
- Standard statistical approaches should be employed
- Bioequivalence Criteria
 - For the primary PK parameters, the 90% confidence interval for the geometric mean ratio should lie within a range of 80.00 - 125.00%

Data Analysis

- Studies where multiple Comparator Products are included
 - Comparator Products are independent and region-specific
- Studies where multiple Test Products are included
 - Application of multiplicity correction depends on the underlying objectives of the study

Special Topics

- Endogenous compounds
- Other IR dosage forms
 - Orally Disintegrating Tablets (ODTs)
 - Chewable Tablets
 - Oral Suspensions
- Fixed Dose Combination (FDC) Products
- pH dependency
 - Absorption of drug substances with pH-dependent solubility may be influenced by the gastric pH

Conclusions

- The harmonised M13A guideline provides recommendations on:
 - BE study design
 - Principles for conducting BE studies
 - BE standards for IR solid oral dosage forms
- This harmonised guideline reduces the need for additional in vivo BE studies and supports streamlined global drug development
- The process of harmonisation will continue with M13B and

THANK YOU!