Final Concept Paper
M13: Bioequivalence for Immediate-Release Solid Oral Dosage Forms
Dated 19 June 2020
Endorsed by the Management Committee on 10 July 2020

Type of Harmonisation Action Proposed

It is proposed to develop a new multidisciplinary guideline.

Statement of the Perceived Problem

Immediate-release (IR) solid oral dosage forms with systemic action, where bioequivalence (BE) is largely established via clinical pharmacokinetic (PK) studies or comparative in vitro dissolution studies, constitute a significant portion of the approved drug products and products under development. BE assessment for these oral dosage forms is important for establishing therapeutic equivalence for generic drug products to their respective comparator products. In addition, application of the BE concept is important for bridging various formulations during new (innovator) drug development. Furthermore, BE studies are used by innovator and generic product developers to bridge certain types of post approval formulation changes.

The BE concept is core to product development and regulatory assessment for generic and new (innovator) products throughout their lifecycle. Although guidelines on BE assessment exist for a majority of regulatory agencies and international health organisations with generally similar approaches to determine BE, there remain some significant differences that hamper global harmonisation of drug development.

Unharmonised BE study design and standards result in product developers having to generate multiple sets of data and information to support marketing authorisation in more than one jurisdiction. This can lead to approval not being sought in some markets due to the additional BE development burden, resulting in a limited availability of drugs in those markets. By contrast, harmonisation could facilitate the use of the same data and information to meet multiple jurisdictions' regulatory requirements and ensures the application of consistent standards for demonstrating BE. In addition, harmonisation may streamline drug development and make it more cost effective, by potentially reducing the number of duplicative BE studies that are required to meet the standards for more than one jurisdiction. Furthermore, this may lead to a reduced number of human subjects that are required for these studies.

Issues to be Resolved

Issues to be resolved in the series of M13 guidelines will include:

- General considerations and principles on BE study design
- Data analysis
- Biowaivers for additional strengths
- Advanced BE study design considerations
- Data analysis and BE assessment for highly variable drugs and drugs with a narrow therapeutic index

We plan to group topics into three tiers with a staggered approach in the timeline of development of series or annexes of the guideline.

Topics in **Tier 1** will constitute the first in the series of the M13 guidelines (e.g., M13A) with a focus on the BE study considerations and data analysis for a non-replicate study design (i.e., different test or comparator products will only be dosed once in the study).

Study design elements will include:

- Crossover vs. parallel
- Single dose vs. multiple dose
- Study population
- Sample size
- Study condition with regard to meal or water
- Dose or dose strength to be studied
- Analyte(s) to be measured (e.g., parent or metabolite, racemate vs. enantiomer)
- Endogenous substances
- Multiple comparator (reference) products in one study
- Multiple test products in one study*

Considerations for data analysis will include but not limited to:

- Statistical methods for BE related to non-replicate study design
- BE criteria
- Handling of outliers
- Long half-life drugs
- Truncated or partial AUC considerations

*This topic may be included in Tier 1 for efficiency but the topic is a low priority and may not be pursued in Tier 1 if the development of a harmonised approach on the topic hampers the overall timeline of M13A.

The topic in **Tier 2** includes biowaiver considerations for additional strengths. This will likely constitute the second guideline in the series of the M13 guidelines (e.g., M13B or as an annex to M13). This topic is important to drug development and should be started as soon as feasible. The development of the Tier 2 topic will commence once the topics included in Tier 1 complete ICH step 1 (consensus building).

Topics in **Tier 3** include data analysis and BE assessment for 1) highly variable drugs, 2) drugs with narrow therapeutic index, and 3) advanced BE study design and data analysis considerations. With progression of Tier 1 and 2 topics, staggering may allow more regular uptake of topics such that topics currently identified in Tier 3 may be brought forward. Tier 3 topics may therefore be developed after the Expert Working Group (EWG) completes the Tier 2 topic or in parallel to the Tier 2 topic, resources permitting. These Tier 3 topics can be included in later guidelines in the series of the M13 guidelines (e.g., M13C) or as annexes to M13.

Acceptance of comparator products across regions could reduce the burden of multiple clinical trials demonstrating BE against local comparators. However, in many territories this is governed by local laws rather than scientific guidelines. Therefore, the "acceptance of

comparator products across regions" is not included in the scope of M13 at this time. However, by including the topic of study designs containing multiple comparator products in the scope of the first guideline in the series of the M13 guidelines, the EWG will be able to take some initial steps to reduce the associated burden without prejudice to regional legislative requirements.

Background to the Proposal

This proposal follows ICH's endorsement of the Reflection Paper, "Further Opportunities for Harmonisation of Standards for Generic Drugs"[1] which proposes development of guidelines to support harmonisation of scientific and technical standards for generic drugs. The proposal is a product of the ICH Generic Drug Discussion Group (GDG) which has worked to reach a consensus on a recommended first guideline effort to harmonise standards for the establishment of BE. The GDG has shared information on regional requirements with respect to BE study design and data analysis for IR solid oral dosage forms and determined that it would be possible and of value to harmonise the proposed elements.

Harmonisation of BE study design and standards would benefit both innovator and generic product developers as the same scientific approach could be followed in multiple jurisdictions, potentially reducing duplicative work. Patients would also benefit as harmonisation would help regulatory agencies in the timely authorisation and availability of quality, safe and effective drugs based upon harmonised acceptance criteria. Furthermore, harmonisation could improve global access to drugs.

Type of Expert Working Group (EWG) and Resources

The EWG should include regulators and industry representatives, in line with existing ICH procedures, being experts in PK and BE with knowledge of associated aspects such as biopharmaceutics, clinical pharmacology, in vitro dissolution and biostatistics. Subject matter experts outside the EWG will be consulted or invited ad hoc, as needed.

Timing

It is proposed to start developing the first harmonised guideline in the series following the endorsement of this concept paper and associated business plan. The expected timeframe for completion of the first guideline of the series, including Tier 1 topics, is three years. To complete all three tiers of topics as outlined in the concept paper will take a longer time (about five to seven years). A more detailed proposal on the development of Tier 2 and Tier 3 topics will be generated by the M13 EWG after completion of Tier 1 topics. The work plan will be discussed with the ICH Management Committee for endorsement.

First Guideline in the Series (M13A)

- Approval of the Concept Paper Outline November 2019
- Establishment of the Informal Working Group February 2020

[1] ICH Reflection Paper: Further Opportunities for Harmonization of Standards for Generic Drugs. https://admin.ich.org/sites/default/files/2019-04/ICH_ReflectionPaper_GenericDrugs_Final_2019_0130.pdf.

- Finalisation of the Concept Paper and Business Plan June 2020
- Approval of Final Concept Paper & Business Plan July 2020
- Teleconferences of EWG July 2020 - until the end of the EWG
- First face-to-face meeting of the EWG November 2020
- Consensus on Technical Document (Step 2a/2b) June 2022
- Adoption of ICH Harmonised Guideline (Step 4) November 2023

Estimated starting time for second guideline in the series or annex July 2022

Estimated starting time for third guideline in the series or annex July 2024