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Considerations regarding the implementation of ICH M13A on bioequivalence for immediate-release solid oral dosage forms

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Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Introduction

ICH M13A Guideline on bioequivalence for immediate-release solid oral dosage forms (EMA/CHMP/ICH/953493/2022) provides recommendations for conducting bioequivalence studies for orally administered immediate-release (IR) solid oral dosage forms designed to deliver drugs to the systemic circulation, such as tablets, capsules, and granules/powders for oral suspension. In addition to new Marketing Authorisation Applications (MAA), ICH M13A will apply to variations to existing authorised medicinal products.

ICH M13A is the first guideline in a foreseen ICH series (ICH M13A, M13B and M13C) describing the scientific and technical aspects of study design and data analysis to support bioequivalence assessment for orally administered IR solid oral dosage forms during both development and post approval phases. For more information on ICH harmonisation of bioequivalence, please refer to the dedicated ICH M13 page.

The purpose of this implementation document is to address specific considerations to enable the practical application of ICH Guideline M13A in the European Union and the transition from the current EMA Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1). This document is intended to provide guidance for Marketing Authorisation Applicants and Marketing Authorisation Holders, Contract Research Organisations, and Regulators.

Background

Six months after its adoption by CHMP, ICH M13A came into effect on 25 January 2025, formally superseding applicable parts of the previously enforced EMA Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1), which had been in effect since 1 August 2010. From this date of coming into effect, stakeholders are required to follow ICH M13A recommendations.

ICH M13A, however, only relates to 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 (see Tier 1 in the ICH M13 Concept Paper - ich.org).

Study design elements in ICH M13A include (but are not limited to): • Crossover vs. parallel • Single dose vs. multiple dose • Study population • Sample size • Sampling schedule • Test and comparator product • 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 • Fixed dose combination and • pH-dependency.

Considerations for data analysis include (but are not limited to): • Statistical methods for BE related to non-replicate study design • Primary pharmacokinetic (PK) parameters • BE criteria • Handling of outliers • Long half-life drugs and • Truncated or partial AUC considerations.

The topic in Tier 2 includes biowaiver considerations for additional strengths. This will constitute the second guideline in the series of M13 guidelines (M13B), which is currently under development.

Topics in Tier 3 (for M13C) include BE study design and data analysis for: • Highly variable drugs (replicate design) • Drugs with narrow therapeutic index, and complex BE study design and data analysis e.g., • Adaptive design and • Handling missing samples.

Implementation

After 25 January 2025, the EMA Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1) pertaining to specific topics not addressed in ICH M13A will continue to apply until such time as they are replaced by new ICH guidance.

It is, therefore, highlighted that the requirements of both ICH M13A and the existing EMA Guideline read in conjunction may be applicable to e.g., • BE studies with highly variable drugs (replicate design) • drugs with narrow therapeutic index, and • complex BE study designs and data analysis e.g., • adaptive design. Therefore, any deviation from either guideline will need to be appropriately scientifically justified.

EMA is reviewing all of its existing Product-specific bioequivalence guidance | European Medicines Agency (EMA), (which are currently to be read in conjunction with the general requirements of EMA Guideline on the investigation of bioequivalence) to determine whether they are compatible with the requirements of ICH M13A and to revise as needed. After 25 January 2025 and pending finalisation of this revision of existing product-specific bioequivalence guidelines (anticipated Q2 2025), EMA product-specific bioequivalence guidelines will also need to be read in conjunction with the requirements of ICH M13 and again, any deviations from the ICH or EMA Guidelines will need to be appropriately scientifically justified.

In addition, after 25 January 2025, the existing Clinical pharmacology and pharmacokinetics: questions and answers | European Medicines Agency (EMA) should also be read in conjunction with ICH M13A until EMA review has been completed and individual Q and As withdrawn as appropriate (again anticipated Q2 2025).

It is expected that the EMA Guideline on the investigation of bioequivalence will be replaced by the ICH series (ICH M13A, M13B and M13C) and withdrawn in due course. EMA, therefore, commits to update this implementation document as the abovementioned harmonisation efforts related to bioequivalence progress.

In what concerns the implementation of ICH M13A requirements for regulatory submissions:

- If BE studies have been completed and included in a regulatory submission (new MAA or post-authorisation applications*)* before 25 January 2025, the requirements of the EMA Guideline remain applicable.
- If you are still in the planning stage for BE studies on 25 January 2025, you should segue to implementing ICH M13A.
- BE studies included in a regulatory submission submitted after 25 January 2025 should follow the requirements of ICH M13A. Any deviation from the requirements (e.g. studies conducted in compliance with EMA guideline and finalised before ICH M13A became effective) should be discussed in the respective application and will be assessed on a case-by-case basis. The Applicant may consider contacting the relevant competent authority to discuss the particular circumstances of the application.