M13A: BIOEQUIVALENCE FOR IMMEDIATE-RELEASE SOLID ORAL DOSAGE FORMS

Step 4 document – to be implemented

Date: 23 July 2024

Legal Notice

Background

- **This document has been signed off as a *Step 4* document (23 July 2024) to be implemented by the ICH Regulatory Members.**

- **This document was developed based on a Concept Paper (10 July 2020) and a Business Plan (10 July 2020).**

Key Principles

- **This new multidisciplinary guideline addresses the conduct of bioequivalence (BE) studies.**

- **This guideline provides recommendations on conducting BE studies during both development and post approval phases 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.**

Key Principles (continued)

- **This guideline, ICH M13A, is the first guideline in the series describing the scientific and technical aspects of study design and data analysis to support BE assessment.**

- **The acceptance of comparator products to be used in BE studies across regions is not in the scope of ICH M13A.**

- **BE studies should be conducted according to the principles and recommendations in ICH E6, *Good Clinical Practice*.**

Guideline Objectives

- **This BE guideline is intended to reduce the need for multiple different sets of data and information from duplicative BE studies to support marketing authorisation in more than one jurisdiction.**

- **This guideline provides recommendations on BE study design and standards for IR solid oral dosage forms.**

- **This guideline will result in the harmonisation of current regional guidelines/guidances, reduce the need for additional in vivo BE studies, and support streamlined global drug development.**

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Summary of Guideline Content

- ## 1.3 Scope
  - M13A is the first guideline in the series to describe the scientific and technical aspects of study design and data analysis to support BE assessment.

  - The second guideline M13B will describe biowaiver considerations for additional strengths.

  - The third guideline M13C will include data analysis for highly variable drugs, drugs with narrow therapeutic index, and complex BE study designs.

Summary of Guideline Content

- **1.3 Scope (continued)**
    - The acceptance of comparator products across regions is not in the scope of M13A.

    - The guideline does not cover aspects to support bioavailability assessment for new drug development in support of intended use or dosing recommendations in drug labelling.

Summary of Guideline Content (continued)

- **2. General Principles in Establishing Bioequivalence**

  2.1 Study Design for Pharmacokinetic Endpoint Bioequivalence Studies:

  - 2.1.1 Study Population
    - The BE study should normally be performed in healthy subjects unless the drug carries safety concerns that make this approach unethical.

Summary of Guideline Content (continued)

2.1 Study Design for Pharmacokinetic Endpoint Bioequivalence Studies: (continued)

- <u>2.1.2 Study Design</u>

    - A randomised, single-dose, crossover study design is recommended when comparing test and comparator formulations.

    - Treatment periods should be separated by a sufficiently long washout period (e.g., > 5 elimination half-lives).

Summary of Guideline Content (continued)

2.1 Study Design for Pharmacokinetic Endpoint Bioequivalence Studies: (continued)

- 2.1.2 Study Design (continued)
  - For safety and/or tolerability reasons, instead of a single dose study in healthy subjects, a single dose or a multiple dose study in patients may be considered.
    - For a multiple dose study, it should be ensured that steady-state is achieved.
    - The washout may overlap between treatment periods, as long as it is ensured that there is no drug carry over at steady-state from the previous treatment.

Summary of Guideline Content (continued)

2.1 Study Design for Pharmacokinetic Endpoint Bioequivalence Studies: (continued)

- 2.1.2 Study Design (continued)
  - For drugs with a long elimination half-life, a parallel design may be employed. In this case, special care should be taken to ensure similar subject demographics in each of the treatment groups.

Summary of Guideline Content (continued)

2.1 Study Design for Pharmacokinetic Endpoint Bioequivalence Studies: (continued)

- 2.1.3 Sample Size for Bioequivalence Studies
  - The number of subjects to be included should be based on an appropriate sample size calculation to achieve a pre-specified power and pre-specified type 1 error.
  - Minimum number of evaluable subjects: 12 for a crossover design or 12 per treatment group for a parallel design.

Summary of Guideline Content (continued)

2.1 Study Design for Pharmacokinetic Endpoint Bioequivalence Studies: (continued)

- 2.1.4 Test and Comparator Products

  - 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.

  - The test product should be representative of the product to be marketed.

Summary of Guideline Content (continued)

2.1 Study Design for Pharmacokinetic Endpoint Bioequivalence Studies: (continued)

- 2.1.4 Test and Comparator Products (continued)
    - The test product should originate from a batch of at least 1/10 of production scale or 100,000 units, whichever is greater, unless otherwise justified. In case of a production batch smaller than 100,000 units, a full production batch is required.
    - Difference in assay content between test and comparator product should be normally within 5%.

Summary of Guideline Content (continued)

2.1 Study Design for Pharmacokinetic Endpoint Bioequivalence Studies: (continued)

- ## 2.1.5 Fasting and Fed Study Conditions
  - The design of a BE study with regard to the 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 as well as the understanding of the properties of drug substance and formulations of the comparator product and the test product (non-high-risk or high-risk).
  - If administration of a single dose of the drug product under either fasting or fed conditions raises safety concerns, the BE study should be conducted under the condition with less safety concerns.

Summary of Guideline Content (continued)

2.1 Study Design for Pharmacokinetic Endpoint Bioequivalence Studies: (continued)

- <u>2.1.5 Fasting and Fed Study Conditions (continued)</u>

  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 or other non-PK reasons.

Summary of Guideline Content (continued)

2.1 Study Design for Pharmacokinetic Endpoint Bioequivalence Studies: (continued)

- 2.1.5 Fasting and Fed Study Conditions (continued)

   High-risk products:

   - Are products where the drug substance characteristics in combination with the complexity of the formulation design or manufacturing process lead to an increased likelihood that *in vivo* performance will be impacted differently between 2 products under fasting and fed conditions.

   - Example of such products: solid dispersions, microemulsions, lipid-based formulations, nanotechnologies, or other specialised technologies.

   - BE studies should be conducted under both fasting and fed conditions.

Summary of Guideline Content (continued)

2.1 Study Design for Pharmacokinetic Endpoint Bioequivalence Studies: (continued)

- <u>2.1.5 Fasting and Fed Study Conditions (continued)</u>

  Standardisation with regard to meals and water:

  - Fasting conditions: fasting should be applied for at least 8 hours. The dose should be administered with 150 – 250 ml water.

  - Fed conditions: start of meal intake 30 minutes before drug administration and the meal should be completely consumed within 30 minutes.

Summary of Guideline Content (continued)

2.1 Study Design for Pharmacokinetic Endpoint Bioequivalence Studies: (continued)

- 2.1.5 Fasting and Fed Study Conditions (continued)

  Standardisation with regard to meals and water: (continued)

  - Fed conditions: (continued)

    - Non-high-risk products: for fed conditions, either a high-fat, high-calorie meal or a low-fat, low-calorie meal is acceptable, unless a specific meal is specified in the product labelling.

    - High-risk products: for fed conditions, a high-fat, high-calorie meal should be applied.

  - The composition of the meal to be administered should be described regarding protein, carbohydrate and fat content.

Summary of Guideline Content (continued)

2.1 Study Design for Pharmacokinetic Endpoint Bioequivalence Studies: (continued)

- <u>2.1.6 Dose or Strength to be Studied</u>

  - In case of an application with multiple strengths, the strength to be used in the BE study depends on the dose proportionality in PK and solubility of the drug substance.

  - In case of dose proportional or more than dose proportional increase in PK: in general, the highest strength should be administered.

  - In case of less than dose proportional increase in PK:

    - if due to saturation of absorption: the lowest strength

    - if due to solubility or unknown reason: the lowest and highest strength

Summary of Guideline Content (continued)

2.1 Study Design for Pharmacokinetic Endpoint Bioequivalence Studies: (continued)

- <u>2.1.7 Moieties to be Measured</u>

  - Demonstration of BE should be based on the analysis of the parent drug.

  - This also applies to pro-drugs, if reliably measurable. Otherwise, the first-step-metabolite may be used.

  - In rare cases, parent drug and primary active metabolite should be considered, e.g., drugs that have metabolites formed through gut wall or gut lumen metabolism that contribute to efficacy or safety.

Summary of Guideline Content (continued)

2.1 Study Design for Pharmacokinetic Endpoint Bioequivalence Studies: (continued)

- 2.1.7 Moieties to be Measured (continued)
  - Enantiomers: BE assessment on the individual enantiomers should be employed in case it is known that:
    - the enantiomers exhibit different pharmacodynamic properties, and
    - the enantiomers exhibit different PK properties, and
    - the exposure (AUC) ratio of enantiomers is modified by a difference in the rate of absorption

Summary of Guideline Content (continued)

2.1 Study Design for Pharmacokinetic Endpoint Bioequivalence Studies: (continued)

- ## 2.1.8 Sampling

  - Sufficient blood samples, including the pre-dose sample, should be taken to obtain a reliable estimation of the absorption phase, the t_{max} and the extent of exposure, which is achieved when $AUC_{(0-t)}$ covers at least 80% of $AUC_{(0-inf)}$.

  - The occurrence of C_{max} at the first post-dose sampling time point should be avoided.

  - For drugs with a long elimination half-life, sampling up to 72h is sufficient.

  - In case an early onset of action is clinically relevant, an additional PK parameter, e.g., pAUC or t_{max}, may be applied to evaluate the early exposure.

Area under the concentration vs. time curve extrapolated to infinity – $AUC_{(0-inf)}$; Area under the concentration vs. time curve from time zero to the time of last quantifiable concentration – $AUC_{(0-t)}$; Maximum concentration after dosing – C_{max} ; Area under the concentration vs. time curve between two specific time points – pAUC ; Time to maximum observed concentration – t_{max}

Summary of Guideline Content (continued)

2.2 Data Analysis for Non-Replicate Study Design:

- <u>2.2.1 Considerations for the Bioequivalence Analysis Population</u>

  - All criteria for study subject inclusion into and exclusion from the BE analysis population should be clearly defined in the study protocol.

  - Data may only be removed from the statistical analysis based on protocol violations which are contemporaneously documented.

  - In exceptional cases, if a subject has in a period an AUC less than 5% of the geometric mean AUC of the product in question, this data may be excluded.

Summary of Guideline Content (continued)

2.2 Data Analysis for Non-Replicate Study Design: (continued)

- 2.2.2 Presentation of Data

  - Drug concentration data should be presented in a tabulated format for each subject participating in the study, along with descriptive statistics.

  - Deviations from the protocol should be clearly identified.

  - Drug concentrations should be measured in accordance with the ICH M10, *Bioanalytical Method Validation and Study Sample Analysis*.

  - Individual and mean concentration-time graphs (linear and log-linear) should be provided.

Summary of Guideline Content (continued)

2.2 Data Analysis for Non-Replicate Study Design: (continued)

- 2.2.2 <u>Presentation of Data (continued)</u>

  - The following single-dose PK parameters should be tabulated:

    - Primary parameters: C_{max}, $AUC_{(0-t)}$ (or $AUC_{(0-72h)}$) and where applicable early exposure data.

    - Additional parameters: $AUC_{(0-inf)}$, $AUC_{(0-t)}/AUC_{(0-inf)}$, t_{max}, kel, $t_{1/2}$.

  - $AUC_{(0-t)}$ should cover at least 80% of $AUC_{(0-inf)}$, except in case AUC is measured over 72 hours.

Area under the concentration vs. time curve from time 0 to 72 hours – $AUC_{(0-72h)}$
The apparent terminal elimination rate constant of the drug – k_{el}
Half-life – $t_{1/2}$

Summary of Guideline Content (continued)

2.2 Data Analysis for Non-Replicate Study Design: (continued)

- 2.2.2 Presentation of Data (continued)
  - The following multiple-dose PK parameters (if applicable) should be tabulated:
    - Primary parameters: C_{maxSS}, $AUC_{(0-tauSS)}$
    - Additional parameters: C_{tauSS}, C_{minSS}, C_{avSS}, fluctuation, swing, t_{max}
  - In the exceptional case where a comparator batch within a 5% potency difference compared to the test cannot be obtained, a potency correction may be applied with supporting justification.

Area under the concentration vs. time curve for one dosing interval at steady state – $AUC_{(0-tauSS)}$
Maximum concentration observed during dosing interval at steady state – C_{maxSS}
Minimum concentration observed during dosing interval at steady state – C_{minSS}
Concentration observed at end of dosing interval at steady state – C_{tauSS}
Average concentration observed during dosing interval at steady state (AUC_{0-tau}/tau) – C_{avSS}

Summary of Guideline Content (continued)

2.2 Data Analysis for Non-Replicate Study Design: (continued)

- <u>2.2.3 Statistical Analysis</u>
  - The statistical analyses should include all data for all subjects who provide evaluable data for the products being compared. Any exclusions from BE analysis population should be documented prior to subject sample analysis.
  - The assessment of BE is based on 90% confidence intervals for the geometric mean ratios (test/comparator) for the primary PK parameters under consideration.
  - The statistical model should be pre-specified in the study protocol. *Post hoc* and data-driven adjustments are not acceptable for the primary statistical analysis.

Summary of Guideline Content (continued)

2.2 Data Analysis for Non-Replicate Study Design: (continued)

- 2.2.3 Statistical Analysis (continued)
  - The statistical analysis should take into account the expected sources of variation.
  - Randomised, non-replicate, crossover design studies should be analysed using an appropriate parametric method, e.g., linear model (GLM) or mixed model.
  - A carry-over test is not relevant, as this can be directly addressed by examination of the pre-treatment plasma concentrations in the subsequent period.

Summary of Guideline Content (continued)

2.2 Data Analysis for Non-Replicate Study Design: (continued)

- 2.2.3 Statistical Analysis (continued)

  - If a pre-dose plasma concentration is >5% of the respective C_{max} in that period, the pivotal statistical analysis should exclude these subject data.

  - For parallel studies, the statistical analysis should reflect independent samples. Groups should be balanced for covariates known to affect PK.

  - For multi-group studies, the BE study should be designed to minimise the group effect in the study. BE should be determined based on the overall treatment effect in the whole study population.

  - Heterogeneity of treatment effect across groups should be evaluated (i.e., group by treatment interaction).

Summary of Guideline Content (continued)

2.2 Data Analysis for Non-Replicate Study Design: (continued)

- ### 2.2.4 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%.

- ### 2.2.5 Multiple Comparator and Multiple Test Product Studies

    - In case a study compares one test product and multiple comparator products, multiplicity correction, i.e., alpha adjustment, is not needed, because comparator products are considered independent and region-specific.

Summary of Guideline Content (continued)

2.2 Data Analysis for Non-Replicate Study Design: (continued)

- 2.2.5 Multiple Comparator and Multiple Test Product Studies (continued)
  - In case a study compares multiple test products vs. a comparator product, the need to apply multiplicity correction depends on the underlying objectives:
    - If the objective is to achieve BE for all test formulations versus the comparator product, then no alpha adjustment is needed.
    - If the objective is to show BE for any of the test formulations, then multiplicity adjustment may be needed.

Summary of Guideline Content (continued)

- **3. Specific Topics**

  3.1 Endogenous Compounds
    - The baseline endogenous concentrations should be measured and subtracted from the total concentrations.
    - The exact method for baseline correction should be pre-specified and justified in the study protocol.
    - PK and statistical analyses should be performed on both baseline uncorrected and baseline corrected data. In general, determination of BE should be based on the baseline corrected data.

Summary of Guideline Content (continued)

- **3. Specific Topics**

    3.1 Endogenous Compounds (continued)

    - When considered necessary, administration of a high dose can be considered, to ensure adequate separation of treatment-induced concentrations over baseline.

    - As an alternative, the need for baseline correction may be avoided by enrolling study subjects with low or no production of the endogenous compounds.

Summary of Guideline Content (continued)

3.2 Other Immediate Release Dosage Forms

- 3.2.1 Orally Disintegrating Tablets (ODTs)

  - If the comparator product labelling states that the ODT can be taken with or without water, the test and comparator products should be administered in the BE study without water.

  - For new intended label use/instructions, for BE, the ODT product should be administered according to its intended labelling and compared with the comparator product administered as per its labelling.

  - For orodispersible films, buccal tablets or films, and sublingual tablets, similar principles apply as those for ODTs.

Summary of Guideline Content (continued)

3.2 Other Immediate Release Dosage Forms (continued)

- 3.2.2 Chewable Tablets

  - For chewable tablets, similar principles apply as those for ODTs.

- 3.2.3 Oral Suspensions

  - For tablets, granules, and powders intended for dispersion in a liquid before administration, BE studies should be conducted according to the comparator product labelling.

  - For new intended label use/instructions, for BE, the suspension should be administered according to its intended labelling and compared with the comparator product administered as per its labelling.

Summary of Guideline Content (continued)

3.3 Fixed Dose Combination

- BE should be demonstrated for all components (drugs) in the fixed-dose combination product according to the principles described in this guideline for non-fixed-dose products.

- Failure to demonstrate BE for one component of the fixed-dose combination results in failure to demonstrate BE for the proposed fixed-dose combination product as a whole.

Summary of Guideline Content (continued)

3.4 pH-Dependency

- The absorption of drug substances with pH-dependent solubility may be influenced by the gastric pH.

- This impact on drug absorption can be altered due to the use of, for instance, pH stabilising excipients or a specific salt-form in the formulation.

- Differences in pH stabilising excipients, salt-form or manufacturing process between formulations, may result in a different BE outcome in a gastric pH-altered situation.

- An additional BE study with concomitant treatment of a pH-modifying drug product would generally be necessary to demonstrate BE, unless scientifically justified.

Summary of Guideline Content (continued)

- **4. Documentation**
  - The report of the BE study should include the complete documentation of its protocol, conduct, and evaluation.
  - It should be written in accordance with ICH E3, *Structure and Content of Clinical Study Reports*.

Considerations

- **Guidelines that should be read in conjunction**
  - o ICH M9 Biopharmaceutics Classification System-Based Biowaivers
  - o ICH M10 Bioanalytical Method Validation and Study Sample Analysis
  - o ICH E3 Structure and Content of Clinical Study Reports
  - o ICH E6 Guideline for Good Clinical Practice
  - o ICH E9 Statistical Principles for Clinical Trials

Conclusions

- **This harmonised 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.**

Contact

- **For any questions please contact the ICH Secretariat:**

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