M13B: BIOEQUIVALENCE FOR IMMEDIATE-RELEASE SOLID ORAL DOSAGE FORMS - ADDITIONAL STRENGTHS BIOWAIVER

Step 2

Step 2 document – to be released for comments

Prepared by the ICH M13 Expert Working Group

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International Council for Harmonisation of Technical Requirements
for Pharmaceuticals for Human Use

Legal Notice

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Background

- **This document has been signed off as a *Step 2* document (13 March 2025) to be issued by the ICH Regulatory Members for public consultation**
- **This document was developed based on a Concept Paper (10 July 2020) and a supplemental Concept Paper (2 Mar 2023) and a Business Plan (10 July 2020)**
- **Anticipating finalisation as *Step 4* document to be implemented in the local regional regulatory system: Nov 2026**

Key Principles

- **This proposed new multidisciplinary guideline will address biowaivers of in vivo bioequivalence (BE) studies of additional strengths for orally administered immediate-release (IR) solid oral dosage forms.**
- **This M13B guideline is the second guideline in the M13 series to describe the scientific and technical aspects of demonstrating BE for additional strengths of an oral IR drug product.**

Guideline Objectives

- **This guideline will provide recommendations on obtaining waivers of BE studies for one or more additional strength(s) of a drug product in an application where BE has been demonstrated for at least one of the strengths following ICH M13A.**
- **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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- **Annex II: Decision Tree to Determine the Possibility of an Additional Strength Biowaiver for Non-High-Risk Drug Products**

Summary of Guideline Content

- **1.3 Scope**
  - The M13B guideline is the second guideline in the series to describe biowaiver considerations for additional strengths of an oral IR drug product.
  - M13A was the first guideline in the series to describe the scientific and technical aspects of study design and data analysis to support BE assessment for oral IR drug products.
  - M13C, the third guideline in the series, 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)**
  - M13B describes the additional strength biowaiver criteria relating to:
    - Dose proportionality in PK
    - Formulation proportionality of drug substance and excipients
    - Similarity in dissolution profiles between the biobatch strength(s) and the additional strength(s)
  - The guideline does not discuss in detail alternative approaches to demonstrating BE of additional strengths such as in vitro-in vivo correlations (IVIVCs) or other modelling approaches.

Summary of Guideline Content (continued)

- **2. Criteria for Biowaiver of Additional Strengths**

2.1 PK Dose Proportionality of the Drug.

- The selection of biobatch strength(s) is based on the proportionality in PK of the drug as detailed in the ICH M13A guideline.

2.2 Qualitative and Quantitative Composition Among Different Strengths (Manufacturing and Formulation Aspects).

- 2.2.1 Product composition
  - For a biowaiver, the formulation(s) of the additional strength(s) should be qualitatively the same as that of the biobatch strength.

Summary of Guideline Content (continued)

- **2. Criteria for Biowaiver of Additional Strengths (cont.)**

2.2 Qualitative and Quantitative Composition Among Different Strengths (Manufacturing and Formulation Aspects) (cont.)

- 2.2.1 Product composition (cont.)
  - The composition of the core formulations for the additional strength(s) should be quantitatively proportional to that of the biobatch strength.

    As an exception, deviations from proportionality with an appropriate scientific justification may be considered (see Annex I of the guideline).

Summary of Guideline Content (continued)

- **2. Criteria for Biowaiver of Additional Strengths (cont.)**

2.2 Qualitative and Quantitative Composition Among Different Strengths (Manufacturing and Formulation Aspects) (cont.)

- 2.2.2 High-potency drugs
  - If the amount of drug substance in the formulation is not more than 5% of the drug product core weight in all strengths, a biowaiver for additional strength(s) may be possible if one of the following conditions is met:

Summary of Guideline Content (continued)

- **2. Criteria for Biowaiver of Additional Strengths (cont.)**

2.2 Qualitative and Quantitative Composition Among Different Strengths (Manufacturing and Formulation Aspects) (cont.)

- 2.2.2 High-potency drugs (cont.)
  - the amounts of each excipient in the product core are constant between the additional and biobatch strengths and only the amount of drug substance is changed
  - the amount of diluent/filler varies to account for the change in the amount of drug substance between the additional strength(s) and biobatch strength, while the amounts of other excipients remain constant

Summary of Guideline Content (continued)

- **2. Criteria for Biowaiver of Additional Strengths (cont.)**

2.2 Qualitative and Quantitative Composition Among Different Strengths (Manufacturing and Formulation Aspects) (cont.)

- 2.2.3 Manufacturing Requirements
  - The manufacturing process used for the additional strength(s) should be the same as that used for the biobatch strength.

Summary of Guideline Content (continued)

- **2. Criteria for Biowaiver of Additional Strengths (cont.)**

2.3 Dissolution Conditions (including Optimisation and Validation)

- Similarity of in vitro dissolution should be demonstrated between the additional strength(s) and the biobatch strength(s).
- The same batch(es) used in the BE study(ies) should be used for comparative dissolution testing.

Summary of Guideline Content (continued)

- **2. Criteria for Biowaiver of Additional Strengths (cont.)**

2.3 Dissolution Conditions (including Optimisation and Validation) (cont.)

- The following conditions should be employed
  - Paddle (50 rpm) or basket apparatus (100 rpm)
  - Media volume 900 ml or less and temperature 37±1˚C
  - ≥ 12 units of additional strength and biobatch strength
  - Media pH 1.2, 4.5, 6.8 and QC media
  - No use of surfactant (only in QC media)
  - Samples should be filtered during collection.
  - The use of enzymes may be acceptable in case of capsules or tablets with gelatin coatings.

Summary of Guideline Content (continued)

- **2. Criteria for Biowaiver of Additional Strengths (cont.)**

2.3 Dissolution Conditions (including Optimisation and Validation) (cont.)

- Complete dissolution may not be achievable for all strengths due to limited solubility of the drug substance at a certain pH and therefore, dissolution may differ between strengths.
- To demonstrate that this is due to pH-dependent solubility and not due to formulation factors, similar dissolution can be demonstrated using the same dose in the vessel (e.g., 1 x 15 mg tablet vs. 3 x 5 mg tablets) or by showing the same dissolution behaviour in the comparator product at the same strengths.

Summary of Guideline Content (continued)

- **2. Criteria for Biowaiver of Additional Strengths (cont.)**

2.3 Dissolution Conditions (including Optimisation and Validation) (cont.).

- Other dissolution conditions, e.g., compendial apparatuses and agitation speeds, may be considered to overcome specific issues, e.g., coning, if scientifically justified
- For suspensions, a rotational speed of 50 rpm is recommended with the paddle apparatus, if not otherwise justified.

Summary of Guideline Content (continued)

- **2. Criteria for Biowaiver of Additional Strengths (cont.)**

2.4 Assessment of Similarity

- Dissolution profiles should be properly characterised:
  - Sampling time points should be chosen to adequately describe the complete dissolution profile and depends on reaching the time to reach a plateau.
  - At least three time points are necessary (zero excluded) although more than three time points are preferred, with the final time point occurring when dissolution ≥85% for either the additional strength or biobatch strength product, or just after both strengths have reached a plateau.
  - Dissolution tests and sampling need not exceed 2 hours.
  - Dissolution profiles of additional strength and the biobatch strength should be composed of identical time points. In principle, not more than six time points should be included in the calculations of similarity.

Summary of Guideline Content (continued)

- **2. Criteria for Biowaiver of Additional Strengths (cont.)**

2.4 Assessment of Similarity (cont.)

- Dissolution profile similarity is concluded as follows (see also decision tree in Figure 1 of this guideline):
  - if ≥85% of the drug is dissolved within 15 minutes (very rapid dissolution) for both the additional strength and biobatch strength mean dissolution profiles
  - If ≥85% of the drug is dissolved between 15 minutes and 2 hours for either product being compared and the standard deviation (SD) is ≤8%, and the f_2 factor is ≥50

Summary of Guideline Content (continued)

- **2. Criteria for Biowaiver of Additional Strengths (cont.)**

2.4 Assessment of Similarity (cont.)

- Dissolution profile similarity is concluded as follows (see also decision tree in Figure 1 of this guideline)(cont.):
  - If the SD >8%, the bootstrapping methodology should be used to calculate 90% confidence interval (CI) for the similarity factor; and the lower bound of the 90% bootstrapped CI ≥ 46 and the point estimate (f_2) is ≥ 50.
  - The above-mentioned criteria can also be applied when dissolution is incomplete, i.e., <85% within 2 hours.
  - When the maximum portion dissolved of both the additional strength and biobatch strength plateau is below 10%, similarity can be assumed.

Summary of Guideline Content (continued)

- **3. Specific Topics**

3.1 Fixed Dose Combination Products

- For FDCs that consist of multiple strengths, a biowaiver may be applied for the additional strength(s).
- When a FDC is formulated as a single blend or granulate (monolithic), the conditions regarding direct proportionality should be fulfilled for each individual drug substance in the FDC. When considering the amount of one drug substance in an FDC, the other drug substance(s) can be considered as excipient(s), i.e., as diluent/filler. In this case the proportionality rules should still be fulfilled (see Section 2.2.1 and Annex I of this guideline).

Summary of Guideline Content (continued)

- **3. Specific Topics (cont.)**

3.1 Fixed Dose Combination Products (cont.)

- When an FDC is formulated with the individual drug substances in separate layers, requirements for proportionality in the formulation(s) of the additional strength(s) should follow those of non-FDCs (see Section 2.2.1 and Annex I of this guideline) and should be considered independently for each layer.
- Dissolution data should be submitted for each individual drug substance in the FDC.
- Dissolution similarity between the additional strength(s) and the biobatch strength(s) should be demonstrated.

Summary of Guideline Content (continued)

- **3. Specific Topics (cont.)**

3.2 Bracketing Where the Above Criteria Are Not Met

- Assuming qualitative similarity is maintained between strengths, a bracketing approach may be used when BE assessment at more than two strengths is needed due to one or more of the following reasons:
  - Dissolution dissimilarity between strengths (see Section 2.4 of this guideline)
  - Deviations from direct proportionality in core composition exceeding those described in Annex I of this guideline; or
  - Non-dose proportional PK (see ICH M13A, Section 2.1.6)

Summary of Guideline Content (continued)

- **3. Specific Topics (cont.)**

3.2 Bracketing Where the Above Criteria Are Not Met (cont.)

- If the strengths selected for BE assessment represent the extremes so that any differences in the remaining strength(s) are covered by these extreme strengths, it is sufficient to conduct BE studies on these strengths, i.e., a waiver of BE studies on the strength(s) in between can be applied.
- Where BE assessment is needed under both fasting and fed conditions, and at two strengths due to deviations from formulation proportionality, it may be sufficient to assess BE under both fasting and fed conditions at only one of the strengths.

Summary of Guideline Content (continued)

- **3. Specific Topics (cont.)**

3.3 Drug Substance Instability

- Drug substance instability may preclude its classification within the Biopharmaceutics Classification System, as described in the ICH M9 guideline.
- For the purpose of additional strength biowaiver and to assign acceptable Level 1 or Level 2 deviations from direct proportionality (see Annex I of this guideline), applicants can provide additional data to justify time-dependent high solubility.

Summary of Guideline Content (continued)

- **4. Documentation**

  - The report of the biowaiver of additional strengths should include:
    - The rationale for additional strength biowaiver strategy and biobatch strength(s) selection
    - A tabular listing of the biobatch strength(s) and the additional strength(s) with their qualitative and quantitative compositions. In case of deviations from direct proportionality, a scientific rationale should be provided.
    - A prospective analysis plan for dissolution profile comparison
    - Dissolution results with tabulated individual and mean values as well as individual and mean dissolution profiles of the additional and biobatch strengths.
    - Dissolution similarity results and conclusions

Conclusions

- **This harmonised guideline provides recommendations on obtaining biowaivers of BE studies for one or more additional strength(s) of an oral IR drug product in an application where BE has been demonstrated for at least one of the strengths.**
- **This harmonised guideline reduces the need for additional in vivo BE studies and supports streamlined global drug development.**

Contact

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