



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

Step 4

Step 4 document – to be released for comments

Prepared by the ICH M13 Expert Working Group

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Background

- This document has been signed off as a *Step 4* document (04 August 2026) to be implemented by the ICH Regulatory Members
- This document was developed based on a Concept Paper (19 June 2020), a supplemental Concept Paper (2 Mar 2023) and a Business Plan (19 June 2020)

Key Principles

- **This new multidisciplinary Guideline addresses biowaivers of in vivo bioequivalence (BE) studies of additional strengths for orally administered immediate-release (IR) solid oral dosage forms.**
- **This ICH 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 provides 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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Summary of Guideline Content

- **1.3 Scope**

- The ICH M13B Guideline, the second guideline in the series, describes biowaiver considerations for additional strengths of an oral IR drug product.
- ICH M13A, the first Guideline in the series, described the scientific and technical aspects of study design and data analysis to support BE assessment for oral IR drug products.
- ICH M13C, the third Guideline in the series, will include data analysis and BE evaluation for highly variable drugs and drugs with narrow therapeutic index, and complex BE study designs.

Summary of Guideline Content (continued)

- **1.3 Scope (cont.)**
 - ICH M13B describes the additional strength biowaiver criteria relating to:
 - Dose proportionality in pharmacokinetics (PK)
 - Formulation proportionality of drug substance(s) and excipients
 - Similarity of the method of manufacture
 - Similarity in dissolution profiles between the additional strength(s) and the biobatch 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. Biowaiver Criteria for Additional Strengths**

- 2.1 Selection of Biobatch Strength(s)

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

- 2.2 Qualitative and Quantitative Composition Between Strengths and Manufacturing 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(s).

Summary of Guideline Content (continued)

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

2.2 Qualitative and Quantitative Composition Between Strengths and Manufacturing Aspects (cont.)

- 2.2.1 Product composition (cont.)
 - The composition of the core formulation(s) for the additional strength(s) should be quantitatively proportional to that of the biobatch strength(s).
 - 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. Biowaiver Criteria for Additional Strengths (cont.)**

2.2 Qualitative and Quantitative Composition Between Strengths and Manufacturing Aspects (cont.)

- 2.2.1 Product composition (cont.)
 - 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. Biowaiver Criteria for Additional Strengths (cont.)**

2.2 Qualitative and Quantitative Composition Between Strengths and Manufacturing Aspects (cont.)

- 2.2.1 Product composition (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(s), while the amounts of other excipients remain constant

Summary of Guideline Content (continued)

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

2.2 Qualitative and Quantitative Composition Between Strengths and Manufacturing Aspects (cont.)

- 2.2.2 Manufacturing Process

- The manufacturing process used for the additional strength(s) should be representative of that used for the biobatch strength(s).

Summary of Guideline Content (continued)

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

2.3 Comparative Dissolution

- 2.3.1 Dissolution Conditions
 - 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. Biowaiver Criteria for Additional Strengths (cont.)**

2.3 Comparative Dissolution (cont.)

- 2.3.1 Dissolution Conditions

- The following conditions should be employed
 - Standardised multimedia
 - Paddle (50 rpm) or basket apparatus (100 rpm)
 - Media volume 900 ml or less and temperature $37 \pm 1^\circ\text{C}$
 - Media pH 1.2, 4.5, and 6.8
 - No use of surfactant

Summary of Guideline Content (continued)

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

2.3 Comparative Dissolution (cont.)

- 2.3.1 Dissolution Conditions (cont.)

- The following conditions should be employed (cont.)
 - Quality control (QC) method
 - ≥ 12 replicates of additional strength and biobatch strength
 - Samples should be filtered during collection
 - The use of enzymes may be acceptable in case of gelatin capsules or tablets with gelatin coatings

Summary of Guideline Content (continued)

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

2.3 Comparative Dissolution (cont.)

- 2.3.1 Dissolution Conditions (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 profiles may differ between strengths.
 - To demonstrate that this is due to pH-dependent solubility and not due to formulation factors, similar dissolution profiles can be demonstrated using the same dose in the vessel (e.g., 3 x 5 mg tablets vs. 1 x 15 mg tablet) or by showing the same dissolution behaviour in the comparator product at the same strengths.

Summary of Guideline Content (continued)

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

2.3 Comparative Dissolution (cont.)

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

Summary of Guideline Content (continued)

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

2.3 Comparative Dissolution (cont.)

- 2.3.1 Dissolution Conditions (cont.)

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

Summary of Guideline Content (continued)

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

2.3 Comparative Dissolution (cont.)

- 2.3.2 Assessment of Similarity

- Dissolution profile similarity is concluded as follows (see also decision tree in Figure 1 of this Guideline):
 - If $\geq 85\%$ of the drug is dissolved within 15 minutes (very rapid dissolution) for both the additional strength and biobatch strength mean dissolution profiles
 - If $\geq 85\%$ of the drug is dissolved between 15 minutes and 2 hours for either strength being compared or plateau has been reached for both strengths, and the standard deviation (SD) is $\leq 8\%$ across all time points for both strengths, and the f_2 is ≥ 50

Summary of Guideline Content (continued)

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

2.3 Comparative Dissolution (cont.)

- 2.3.2 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% at any time points, the bootstrapping methodology should be used to calculate the 90% confidence interval (CI) for the similarity factor; and the lower bound of the 90% bootstrapped CI ≥ 46 and the median f_2 is ≥ 50 .
 - When mean dissolution of both the additional strength and biobatch strength plateau below 10%, similarity can be assumed.

Summary of Guideline Content (continued)

- **3. Specific Topics**

3.1 Fixed Dose Combination Drug 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 if it were an excipient(s), i.e., as if it were a separate diluent(s)/filler(s). In this case the proportionality conditions should still be met (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 Drug Products (cont.)

- When an FDC is formulated with the individual drug substances in separate layers, conditions 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 When In Vivo BE is Needed at Multiple Strengths

- In vivo BE assessment at multiple strengths is needed when one or more of the following conditions apply:
 - Dissolution dissimilarity between strengths (see Section 2.3.2 of this Guideline)
 - Deviations from direct proportionality in core formulation exceeding those described in Annex I; or
 - Non-dose proportional PK under certain circumstances described in ICH M13A, Section 2.1.6

Summary of Guideline Content (continued)

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

3.2 When In Vivo BE is Needed at Multiple Strengths (cont.)

- Where in vivo BE assessment is needed under both fasting and fed conditions and at multiple strengths, assessment of BE for only one strength under both conditions may be sufficient. For the other strengths, a non-high-risk situation may be assumed, and a waiver of either the fasting or fed BE study may be applied with an appropriate justification.
- The condition selected (fasting or fed) to conduct BE for the second strength should follow the principles described in ICH M13A, Section 2.1.5.

Summary of Guideline Content (continued)

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

3.2 When In Vivo BE is Needed at Multiple Strengths (cont.)

- 3.2.1 Bracketing
 - Assuming qualitative similarity is maintained between strengths, a bracketing approach may be used when BE assessment at multiple strengths is needed as described before in Section 3.2

Summary of Guideline Content (continued)

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

3.2 When In Vivo BE is Needed at Multiple Strengths (cont.)

- 3.2.1 Bracketing (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., biowaiver(s) for the intermediate strength(s) is possible.

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 strengths biowaivers 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 strengths 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
 - The measured pH of each medium at the beginning and end of each dissolution run.
 - 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

Summary of Guideline Content (continued)

- **Annex I: Considerations for Deviation from Direct Compositional Proportionality**
 - Deviations from direct proportionality in core formulations between strengths can be considered as exceptions with appropriate scientific justification (see Annex III, Figure 2).
 - For non-high-risk products, containing high solubility drug substance(s), deviations up to Level 2 differences (see Table 1) can be considered if:
 - The total core weight of the additional strength does not deviate by more than 20% from the theoretical total core weight of the additional strength assuming direct proportionality
 - Similarity in mean dissolution profiles is demonstrated with the QC method and under standardised multimedia conditions

Summary of Guideline Content (continued)

- **Annex I: Considerations for Deviation from Direct Compositional Proportionality (cont.)**
 - For non-high-risk products, containing BCS low solubility drug substance(s), deviations up to Level 2 differences (see Table 1) can be considered if:
 - Similar dissolution is demonstrated with the QC method
 - Rapid or very rapid dissolution is demonstrated in at least one of the standardised media conditions (see Section 2.3.1); and
 - The total core weight of the additional strength does not deviate by more than 20% from the theoretical total core weight of the additional strength assuming direct proportionality
 - Similarity in mean dissolution profiles is demonstrated with the QC method and under standardised multimedia conditions

Summary of Guideline Content (continued)

- **Annex I: Considerations for Deviation from Direct Compositional Proportionality (cont.)**
 - Deviations up to Level 1 differences (see Table 1) can be considered if:
 - Similar dissolution is demonstrated with the QC method
 - Sufficient, *i.e.*, at least 10%, mean dissolution is observed to allow f_2 profile comparison under at least one standardised multimedia condition other than the QC condition; and
 - The total core weight of the additional strength does not deviate by more than 10% from the theoretical total core weight of the additional strength assuming direct proportionality
 - Similarity in mean dissolution profiles is demonstrated with the QC method and under standardised multimedia conditions

Summary of Guideline Content (continued)

- **Annex I: Considerations for Deviation from Direct Compositional Proportionality (cont.)**
 - For high-risk products, containing BCS low solubility drug substance(s):
 - Because of the complexity of the formulations using formulation-manufacturing (process/technology) to enhance PK performance, excipients functioning as the solubilising or carrier matrix in the formulation, e.g., the dispersing excipient(s) in a solid dispersion formulation, should be directly proportional to the drug substance(s) between the additional and biobatch strengths. In case a solid dispersion intermediate is applied, proportional amounts of the same intermediate should be used in the different strengths.
 - Deviations up to Level 1 differences (see Table 1) of the remaining excipients can be considered if:
 - Rapid or very rapid dissolution is demonstrated in at least one standardised multimedia condition and with the QC method
 - The total core weight of the additional strength does not deviate by more than 10% from the theoretical total core weight of the additional strength assuming direct proportionality
 - Mean dissolution profile comparison should demonstrate similarity in the standardised multimedia conditions and with the QC method.

Summary of Guideline Content (continued)

- **Annex II: Examples of Application of Additional Strengths Biowaiver Principles**
 - Six theoretical examples are included to illustrate the principles described in the Guideline:
 - Example 1: Direct proportional of core formulations
 - Example 2: Acceptable Level 1 deviation from direct proportionality of core formulations
 - Example 3: Level 1 deviation from direct proportionality of core formulation that does not meet criteria
 - Example 4: FDC direct proportionality of core formulations
 - Example 5: FDC that can be considered proportional for core formulations
 - Example 6: Example of bracketing approach for an FDC

Summary of Guideline Content (continued)

- **Annex III: Decision Tree for Additional Strengths Biowaiver for Non-High-Risk Drug Products**
 - The decision tree included in Figure 2 should be followed to determine whether a biowaiver is possible for an additional strength for non-high-risk drug products.

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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