

M13B: BIOEQUIVALENCE FOR IMMEDIATE-RELEASE SOLID ORAL DOSAGE FORMS

ADDITIONAL STRENGTHS BIOWAIVER

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BioBridges 2026

September 24–25 ● Prague, Czech Republic



Viatriis at a Glance



Formed in 2020 from the combination
of two strong legacy companies



\$14.3 billion in 2025
total revenues



27 manufacturing, packaging and
distribution sites worldwide



~30,000 colleagues across
almost 70 countries



10+ therapeutic areas addressed



10 development centers executing
multiple technology platforms



Headquartered in the U.S.



~1,300 approved molecules



Reach 165+ countries and territories



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Additional sources: **ICHM13B Q&A** and **ICHM13B Guideline**



Two things I know

It's nice to be back to Biobridges

I am going to learn new things about M13B today!

01 ICH M13B

02 ICH M13 series

ICH M13B

Let's dive into it!



Me in Yucatán, Mexico, 2025
(photo taken by Joram Mennes)

ICH M13B

BIOEQUIVALENCE FOR IMMEDIATE RELEASE SOLID ORAL DOSAGE FORMS - ADDITIONAL STRENGTHS BIOWAIVER (M13B) Final version Adopted on 04 August 2026 – **focus of this presentation**

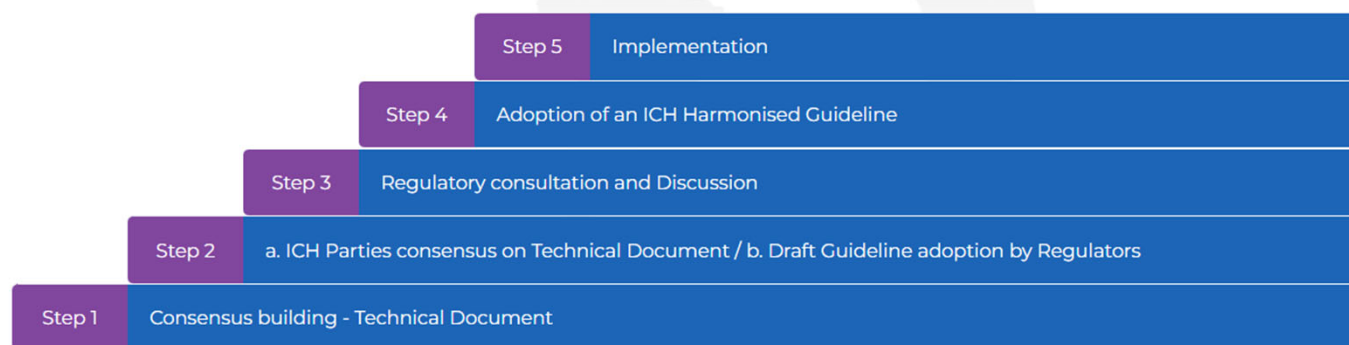
BIOEQUIVALENCE FOR IMMEDIATE RELEASE SOLID ORAL DOSAGE FORMS
Questions and Answers M13B Q&As Adopted on 04 August 2026

Don't forget the Q&A



Formal ICH Procedure

The Formal ICH Procedure is a step-wise procedure consisting of 5 steps (see below, click to have information on a particular step). This procedure is followed for the harmonisation of all new ICH topics.



Step 4: Adoption of an ICH Harmonised Guideline

Step 4 is reached when the Assembly agrees that there is sufficient consensus on the draft Guideline.

The *Step 4* Final Document is adopted by the ICH Regulatory Members of the ICH Assembly as an ICH Harmonised Guideline at *Step 4* of the ICH process.

Step 5: Implementation

Having reached *Step 4*, the harmonised Guideline moves immediately to the final step of the process that is the regulatory implementation. This step is carried out according to the same national/regional procedures that apply to other regional regulatory guidelines and requirements, in the ICH regions.

Implementation status

- Go to www.ich.org, work products (multidisciplinary guidelines) select the guideline you are interested in and check
- <https://www.ich.org/page/ich-guideline-implementation>



17 September 2026
EMA/CHMP/ICH/85092/2025
Committee for Human Medicinal Products



ICH M13B Guideline on bioequivalence for immediate-release solid oral dosage forms - additional strengths biowaiver

Step 5

Transmission to CHMP	13 March 2025
Adoption by CHMP	27 March 2025
Release for public consultation	9 April 2025
Deadline for comments	9 July 2025
Final adoption by CHMP	17 September 2026
Date for coming into effect	17 March 2027

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 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.

Q&A

1.1 How is ICH M13B different from ICH M9 in principle?

Summary of Guideline Content (continued)

1.3 Scope (cont.)

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).

Q&A

2.1	What scientific justification is appropriate to explain deviations from compositional proportionality?
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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:
 - 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.

Q&A

2.2	ICH M13B states “The same batch(es) used in the BE study(ies), or in the pivotal clinical trials for a new drug development, should be used for comparative dissolution testing”. In a case where the biobatch is not available, are other batches acceptable and under which conditions?
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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
 - Standardised multimedia
 - Paddle (50 rpm) or basket apparatus (100 rpm)
 - Media volume 900 ml or less and temperature $37\pm1^{\circ}\text{C}$
 - **Media pH 1.2, 4.5, and 6.8**
 - No use of surfactant
 - 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

Q&A

2.6	Can centrifugation be employed instead of filtration?
2.7	When would it be appropriate to employ more than 12 replicates in a dissolution test?

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.

Q&A

2.3

Do you need to consider the **characteristics of the comparator product** when assessing an additional strengths biowaiver for a drug product?

Q&A

2.4	If differences in dissolution profiles between strengths are due to solubility limitations, ICH M13B recommends testing the same dose per vessel to demonstrate similarity in profiles under those conditions. A. What options are available in cases where equivalent doses cannot be achieved by comparing multiple units of a lower strength to a single unit of the higher strength being compared? B. ICH M13B indicates that the use of multiple units in a dissolution vessel may not be feasible due to an excessive number of individual units in the vessel. How many units are considered to be excessive?
2.5	If differences in dissolution profiles between strengths are due to solubility limitations, ICH M13B recommends testing the same dose per vessel to demonstrate similarity in profiles under those conditions, or if that is not feasible, to demonstrate the same dissolution trend in the comparator product at the same strengths. What is needed to demonstrate similarity in dissolution in these situations?

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

Q&A

2.8	ICH M13B indicates that other dissolution conditions, e.g., compendial apparatuses and agitation speeds, may be considered to overcome specific issues, e.g., coning, if scientifically justified. Can you provide some examples of when other dissolution conditions might be accepted?
2.9	ICH M13B indicates that comparative dissolution studies should be conducted in three compendial media covering the range of pH 1.2 – 6.8 (at or about pH 1.2, 4.5, and 6.8). How far and under what circumstances can the pHs of the dissolution media deviate from pH 1.2, 4.5, and 6.8?

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.

Q&A

2.10	ICH M13B states that sampling time points should be selected to have meaningful contributions to the calculated estimate of the difference between the additional strength and the biobatch strength. How should this be interpreted in selecting sampling time points for a dissolution experiment?
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The selection of sampling time points is dependent on the performance characteristics of the products under investigation. The sampling protocol should be designed to capture the profiles up to completion of dissolution, *i.e.*, the time taken to reach 85% dissolution (or a plateau), with approximately six time points when feasible.

The following scenarios are provided for consideration during the design of a dissolution study, but as noted above, the final design is dependent on the dissolution characteristics of the drug product being investigated and different sampling times could be used, provided the conditions for evaluable time points are met. Inclusion of the 15-minute sampling time point in the protocol is of strategic importance for profile similarity determinations (except in cases of slow dissolution as in scenario 3 below).

1. The dissolution is completed within 30 minutes (rapidly dissolving).

- The suggested sampling times are 5, 10, 15, 20, 30 and 45 minutes.

2. The dissolution is not rapidly dissolving (> 30 minutes) but completed within 45 minutes.

- The suggested sampling times are 10, 15, 20, 30, 45 and 60 minutes.

3. The dissolution is slow, being completed only after 45 minutes.

- The suggested sampling times are 15, 30, 45, 60, 90, and 120 minutes.

Q&A

2.11	Why does ICH M13B recommend including not more than six sampling time points in the f2 calculation for similarity?
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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 **f2 is ≥ 50**

Summary of Guideline Content (continued)

2. Biowaiver Criteria for Additional Strengths (cont.)

2.3 Comparative Dissolution (cont.)

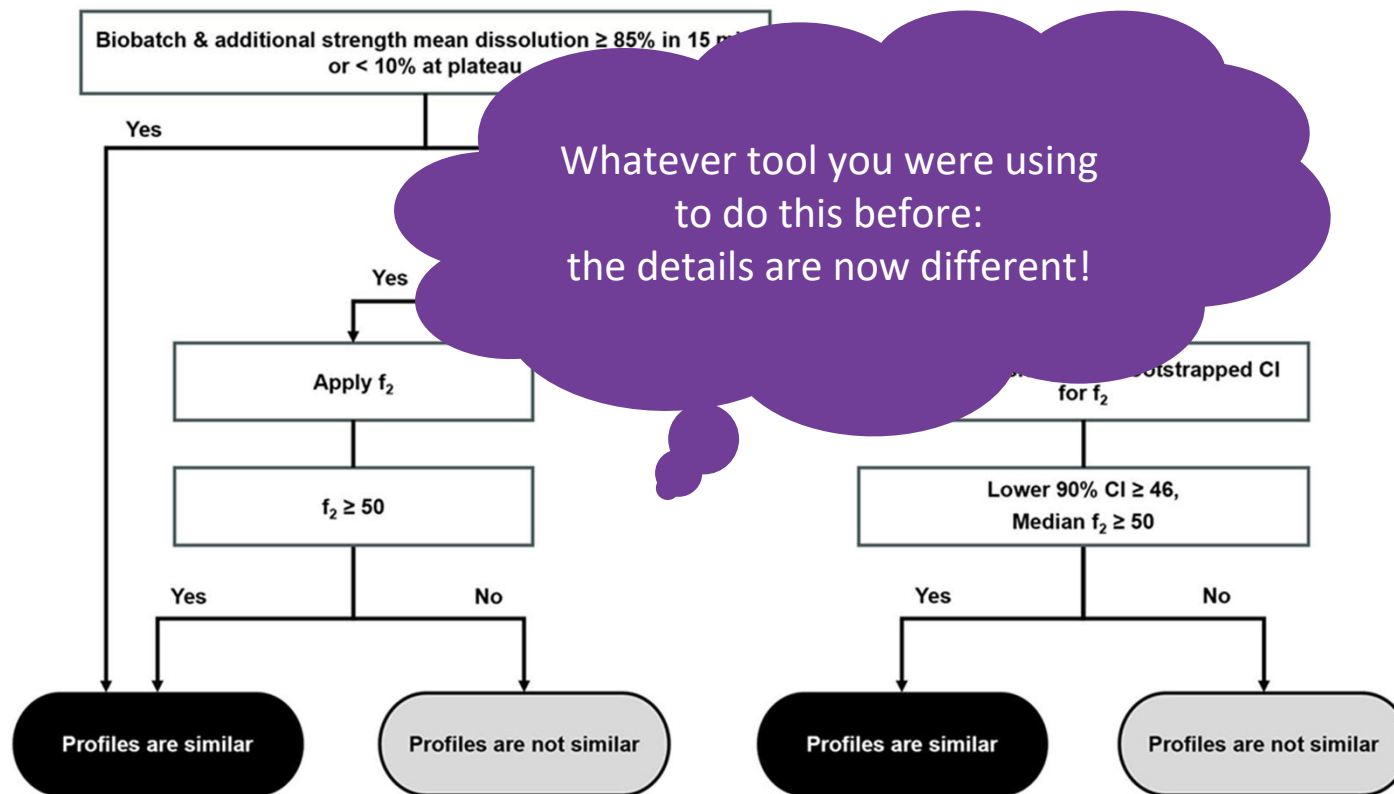
2.3.2 Assessment of Similarity (cont.)

- 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.**

Q&A

2.12	When determining dissolution profile similarity using f2, ICH M13B defines high variability as an SD >8% at any time point. How was this decided, and why was SD used in the definition instead of CV?
2.13	How should dissolution similarity be evaluated if SD >8%, e.g., the type of point estimator and CI, number of bootstrapped data sets, and criteria applied to each individual bootstrapped data set?
2.14	Why does ICH M13B specify 46 as the cut-off for acceptability for the lower bound of the bootstrapped CI for f2 when determining dissolution profile similarity using f2? Why was 50 not used?
2.15	Why does ICH M13B not consider other statistical methods to demonstrate dissolution similarity?

Figure 1



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**.

Q&A

3.1	For the purpose of BCS solubility classification, ICH M9 expects that stability be maintained over relevant timeframes to accommodate the expected duration of absorption, and instability resulting in >10% degradation precludes classification within the BCS. On the other hand, ICH M13B will accept provisional BCS solubility classification for the purpose of application of an additional strengths biowaiver if high solubility is established for the same duration as for the dissolution experiments supporting the biowaiver. Why does this difference exist?
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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

Q&A

A.1	Q&A 2.1 is also applicable to Annex I.
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2.1	What scientific justification is appropriate to explain deviations from compositional proportionality?
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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

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.

Impact of ICH M13B

Much broader than bioequivalence alone!

It also impacts:

- development strategies
- formulation decisions
- regulatory approaches
- and post-approval changes



Who needs to be trained?

Ongoing and future work – M13C

Scope

Tier 3 (M13C guideline) will include:

- BE study design and data analysis for:
 - 1) Highly variable drugs
 - 2) Narrow therapeutic index drugs
 - Complex BE study design and data analysis
 - Adaptive design
 - Other examples (e.g., handling missing samples)
-
- Consensus on Technical Document for M13C (Step 2a/2b) June 2027*
 - Adoption of ICH Harmonised Guideline M13C (Step 4) February 2029

Supplement to the “M13: Bioequivalence for Immediate-Release Solid Oral Dosage Forms” Concept Paper M13C
Dated 13 December 2024, endorsed by the Management Committee on 27 January 2025

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Susana Almeida ✓ • You

Clinical Pharmacologist

4w •

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The Step 4 ICH M13B Guideline and Q&A have now been published, marking an important milestone for our industry.

I am proud to have contributed to a guideline that will shape not only how bioequivalence is assessed, but also how products are developed and managed throughout their lifecycle.

While M13B is often viewed through a bioequivalence lens, its implications extend much further, influencing development strategies, formulation decisions, regulatory approaches, and post-approval changes. For that reason, I encourage colleagues working across these areas to take a look and share it within their networks.

It was a pleasure to work alongside [Russ Rackley](#) and [Zhengguo Xu](#) in bringing the voice of the [IGBA - International Generic and Biosimilar medicines Association](#) to the drafting process.

I also look forward to continuing our efforts with the ICH M13 Expert Working Group as we progress M13C and further advance the harmonization of immediate-release bioequivalence requirements.

A rewarding journey and an exciting step forward for global regulatory harmonization.



Lei Zhang, Ph.D., FAAPS • 1st

Deputy Director at Office of Research and Standards, Office of Generic Drugs, CDER, ...
1mo •

A Major Milestone for Global Drug Development!

The final ICH M13B Guideline — "Bioequivalence for Immediate-Release... more



Thank You



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.)

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 f2 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 solubilizing 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.