U.S. FOOD & DRUG ADMINISTRATION

FDA Webinar

Navigating the Draft ICH M13B Additional Strengths Biowaiver Guideline

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Outline

- Objectives of the webinar
- Overview of ICH M13 guideline series
- Highlights of M13B draft guideline
  - Overview of content
  - Major differences between draft M13B and FDA's current draft ANDA PK BE guidance*
  - Additional discussion on selected topics
- Summary
- Panel discussion
- Audience Q & A
- Closing remarks

ICH: The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; ANDA: Abbreviated New Drug Application; BE: Bioequivalence

* *Guidance for Industry: Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application (Aug 2021)*

Webinar Objectives

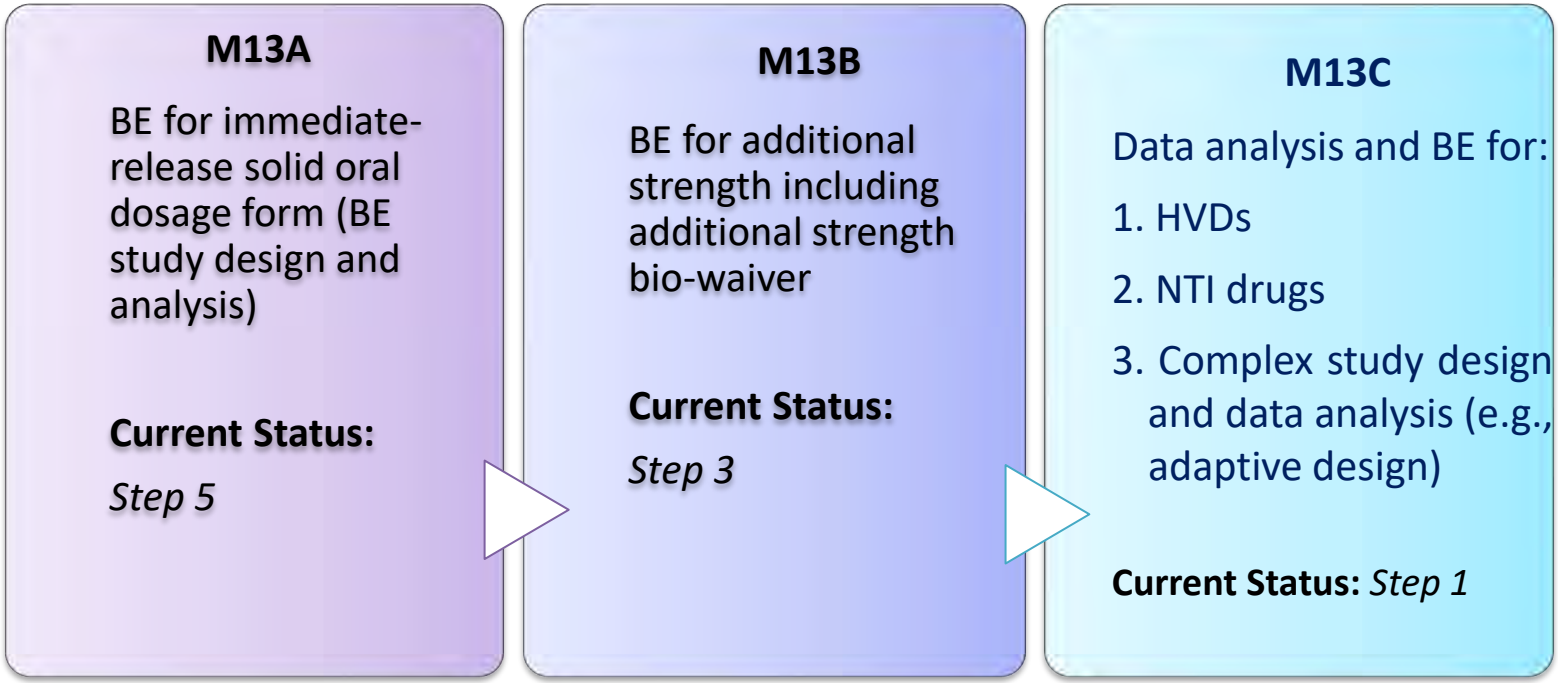
- Provide an overview of the draft ICH M13B guideline
- Explain the ICH Expert Working Group's current scientific thinking behind the guideline
- Highlight main areas that differ from FDA's current guidance on selected topics and their impact
- Clarify the rationale for the guideline's recommendations
- Explain the process for submitting public comments on the draft guideline

Background

- Generic drugs comprise a significant portion of the pharmaceutical market
- Bioequivalence (BE) assessment is important for establishing therapeutic equivalence for generic drug products to their respective comparator products
- ICH Reflection Paper on "*Further Opportunities for Harmonisation of Standards for Generic Drugs*" (endorsed by ICH in Nov 2018) outlines a strategic approach for developing and enhancing ICH guidelines to support the harmonization of scientific and technical standards for generic drugs
  - From non-complex to more complex products
- Common standards for global development for generics can improve access to generic medicines

M13 Guideline Series

- M13 is the first ICH guidance topic that is focused on BE for generic drugs: immediate-release (IR) solid oral dosage forms
- The M13 topic consists of 3 guidelines: M13A, M13B and M13C



HVD: highly variable drug;
NTI: narrow therapeutic index

M13 Guideline Series and Timeline

M13A

- Started: Jul 2020
- *Step 1*: Dec 9, 2022
- *Step 2*: Dec 20, 2022
- Step 4: July 23, 2024
- **Current Status:** *Step 5;* FDA started implementation in Oct 2024
- >800 PSG revisions since Oct 2024

M13B

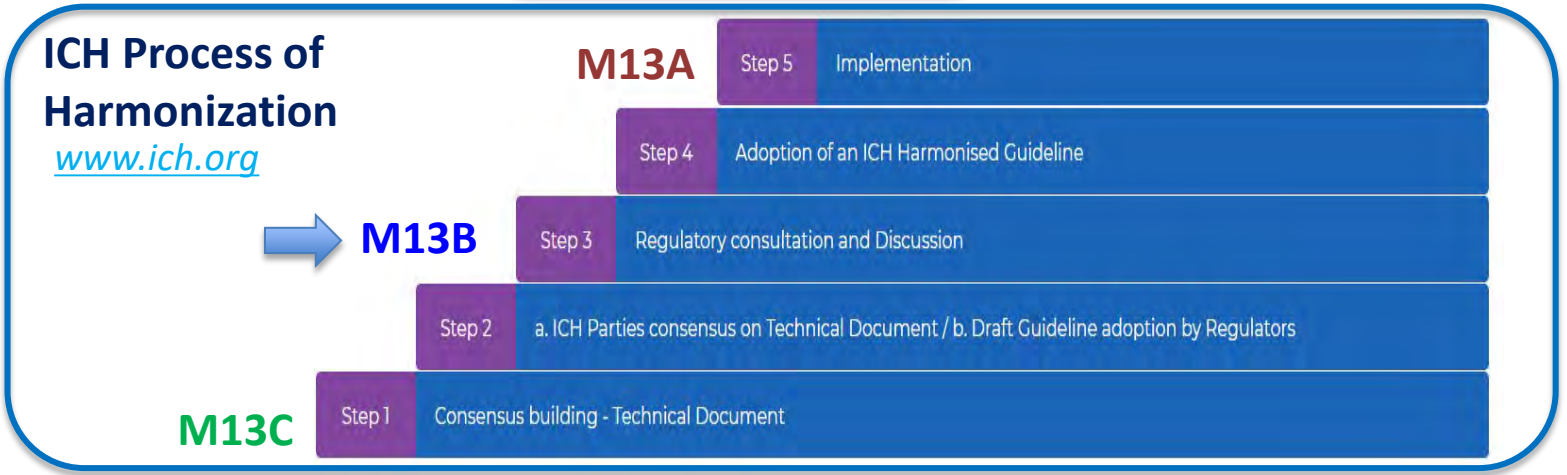
- Started: Nov 2022
- *Step 1:* Feb 12, 2025
- *Step 2*: March 13, 2025
- **Current Status:** *Step 3*
- *Step 4 (est.): June 2026*

M13C

- Started: Feb 2025
- **Current Status:** Draft technical document under development towards consensus
- *Step 2 (est.): June 2027*

ICH Process of Harmonization

www.ich.org



M13B

- Draft guideline has been under public consultation for comments since May 2025
  - https://www.fda.gov/regulatory-information/search-fda-guidance-documents/m13b-bioequivalence-immediate-release-solid-oral-dosage-forms-additional-strengths-biowaiver
  - First deadline: Aug 1, 2025
  - FDA's docket was re-opened on Sept 9 to collect comments
  - Send comments **by Oct 9, 2025**
    - Docket number: FDA-2023-D-0093

M13B Public Consultation Dates

- **ANVISA, Brazil** - Deadline for comments by 30 June 2025
- **EC, Europe** - Deadline for comments by 9 July 2025
- **FDA, United States** - Deadline for comments **by 9 October 2025**; FDA-2023-D-0093
- **HSA, Singapore** - Deadline for comments by 15 June 2025
- **Health Canada, Canada** - Deadline for comments by 31 August 2025
- **JFDA, Jordan** - Deadline for comments by 24 June 2025
- **MFDS, Republic of Korea** - Deadline for comments by 7 June 2025
- **MHLW/PMDA, Japan** - Deadline for comments by 13 June 2025
- **MHRA, UK** - Deadline for comments by 31 July 2025
- **NMPA, China** - Deadline for comments by 30 June 2025
- **SFDA, Saudi Arabia** - Deadline for comments by 13 July 2025
- **Swissmedic, Switzerland** - Deadline for comments by 9 July 2025
- **TFDA, Chinese Taipei** - Deadline for comments by 31 July 2025

Focus of Today's Webinar: M13B

- 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
- This guideline provides recommendations on obtaining waivers of BE studies for one or more additional strength(s) of oral IR 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 harmonization of the current regional guidelines/guidances, reduce the need for additional in vivo BE studies, and support streamlined global drug development

M13B Table of Contents

- **1. Introduction**
  - 1.1 Objective
  - 1.2 Background
  - 1.3 Scope

- **2. Criteria for Biowaiver of Additional Strengths**
  - 2.1 PK Dose Proportionality of the Drug
  - 2.2 Qualitative and Quantitative Composition Among Different Strengths (Manufacturing and Formulation Aspects)
    - Product Composition (Annex I: high risk or non-high-risk*)
    - High-potency Drug Products
    - Manufacturing Process
  - 2.3 Dissolution Conditions (including Optimization and Validation)
  - 2.4 Assessment of Similarity

PK: Pharmacokinetic

*Per M13A: "Risk" refers to risk of bio-inequivalence due to food effect.

M13B Table of Contents (Cont'ed)

- **3. Specific Topics**
  - 3.1. Fixed Dose Combination Products
  - 3.2. Bracketing Where the Above Criteria Are Not Met
  - 3.3 Drug Substance Instability
- **4. Documentation**
- **5. Glossary**

Annex I: Considerations for Deviation from Direct Compositional Proportionality

Annex II: Decision Tree to Determine the Possibility of an Additional Strength Biowaiver for Non-High-Risk Drug Products

M13B Scope

- 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.
  - Applicants are encouraged to consult the regulatory authority(ties) when an alternative approach is proposed or taken

Criteria for Waivers of Additional Strength(s) & Major Differences in Recommendations between Draft M13B and the Draft FDA ANDA BE Guidance (Aug 2021)*

* *Guidance for Industry: Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application (Aug 2021)*

Criteria for Additional Strength(s) Biowaiver

No change from the FDA Guidance, in the general principles

Waiver of additional strengths are based on demonstrating:

- BE for at least one of the strengths via in vivo study (ies)
    - The selection of biobatch strength(s) is based on the dose proportionality in PK of the drug as detailed in ICH M13A
- Formulation proportionality across all strengths
- Comparative dissolution between additional strengths and the bio-strength

Major Differences—1
(Formulation Proportionality, Section 2.2)

- Recommends that the core* formulation be in **direct** proportion between strengths. Deviations beyond level 1 may be considered only for certain non-high-risk** drug products

* Core formulation (M13B): Active and inactive ingredients that make up a drug product, not including tablet film coating or capsule shell

**Per M13A: Risk refers to risk of bio-inequivalence due to food effect (refer to M13A for details)

Formulation Proportionality

Current FDA Draft ANDA BE Guidance	Draft ICH M13B (Section 2.2.1 and Annex 1)
All active and inactive ingredients are in **similar*** proportion between different strengths	All active and inactive ingredients are in **direct** proportion between different strengths
Deviations from *proportional similarity* can be considered with adequate justification The guidance does not include specific recommendation for deviations related to high-risk products	Deviations are considered as **exceptions** Factors considered for allowable deviations are based on: 1. solubility of drug substance 2. complexity of formulation and manufacturing characteristics (high-risk products; M13A) 3. dissolution characteristics of drug product 4. deviations in core weight of additional strength(s)
Proportion of excipients is expressed as percent w/w of **total** formulation	Proportion of excipients is expressed as percent w/w of **core** formulation

* Dissolution Testing of Immediate Release Solid Oral Dosage Forms (August 1997) https://www.fda.gov/media/70936/download

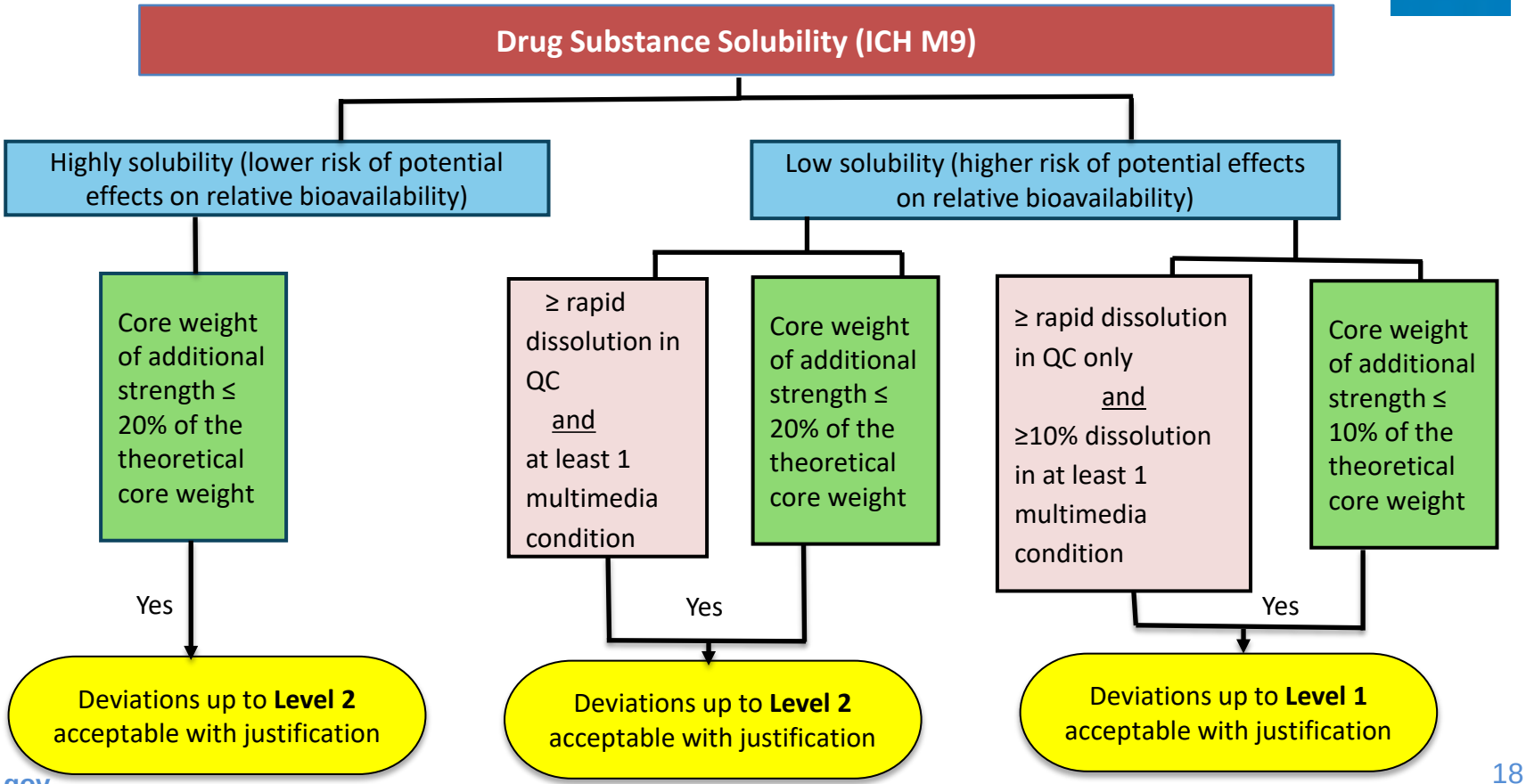
High-Potency Drugs (Section 2.2.2)

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:

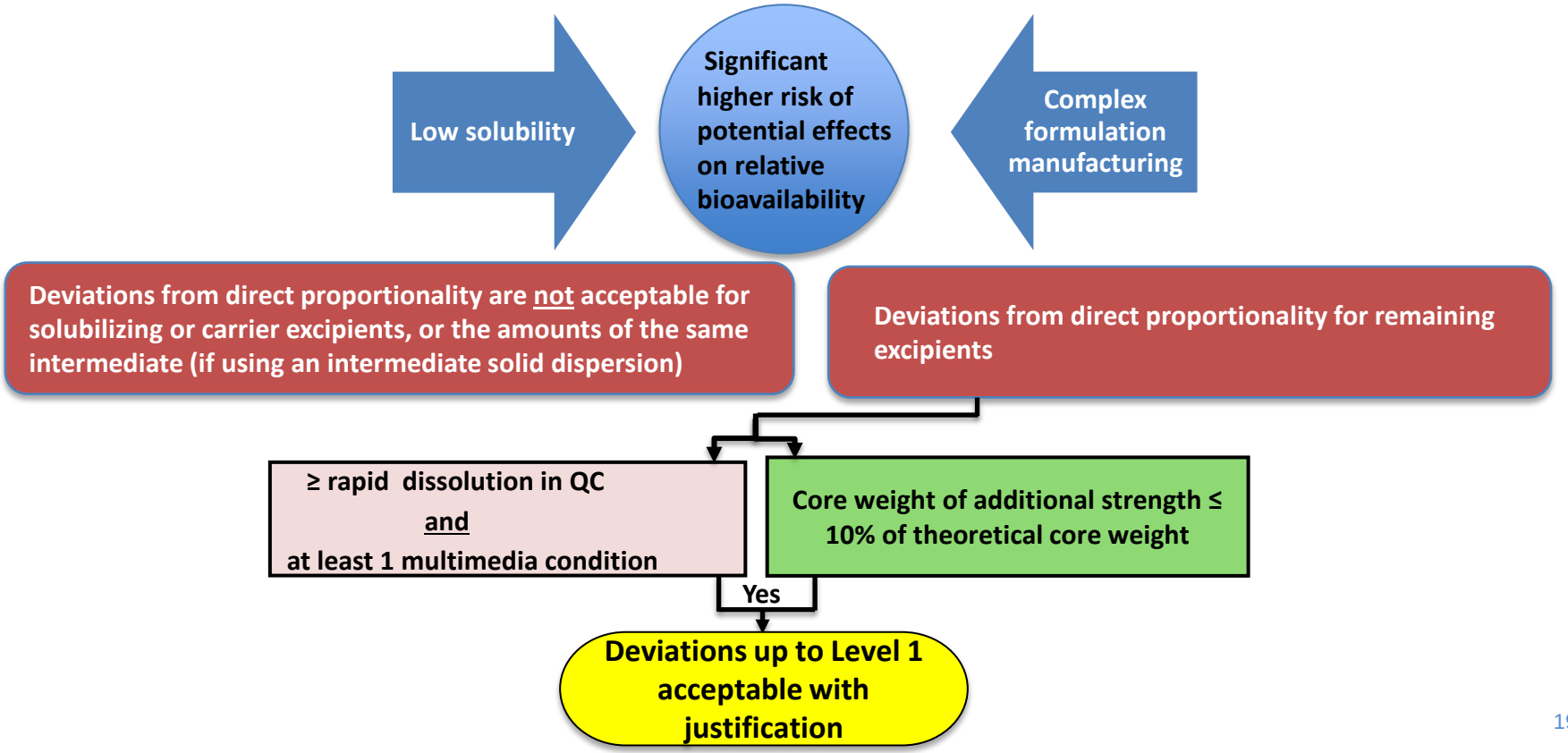
- the amounts of each excipient in the product core are constant between the additional and biobatch strengths and only the amount of drug substance is changed

- the amount of a diluent/filler varies to account for the change in the amount of drug substance (or solid dispersion intermediate, if applicable)

Considerations for Deviations from Direct Proportionality (Non-High-Risk, Non-High-Potency Drugs)



Considerations for Deviations from Direct Proportionality (High-Risk Drugs, Non-High-Potency Drugs)



Acceptable Differences in Excipients between Strengths

- Acceptable differences for Level 1 and Level 2 (also see Table 1; M13B) are based upon SUPAC principles

- Excipients with functions not described in the table, e.g., surfactant should be in direct proportion between strengths. Deviations are generally not allowed and will need additional supporting information to adequately bridge to the biobatch strength

Acceptable Differences for Levels 1 and 2

Function of excipient	Deviation (% w/w)	
	Level 1	Level 2
Diluent/Filler	5	10
Disintegrant		
Starch	3	6
Other	1	2
Binder	0.5	1
Lubricant		
Stearate salts	0.25	0.5
Others	1	2
Glidant (fluidizing agent)		
Talc	1	2
Other	0.1	0.2
Total absolute value of excipient changes	5	10

Understanding the Impact of the Major Differences

Formulation Proportionality

- Guideline criteria in M13B was supported by a retrospective review of more than 700 FDA-approved applications (NDAs and ANDAs) of additional strength biowaiver over a two-year period
  - Greater than 80% of the submissions were formulated with direct proportionality between strengths
  - For ~15% of the submissions, cumulative total differences were within 10%
  - For ~3% of the submissions, justification for lack of proportional similarity were found acceptable

Presumed Impact:
Medium to High

Major Differences—2
(Dissolution Conditions, Section 2.3)

- Recommends multimedia dissolution testing without surfactant for all strengths of the Test product

Dissolution Conditions

Current FDA Draft ANDA BE Guidance and the accompanying Dissolution* and BA Guidance**	Draft ICH M13B (Section 2.3)
Dissolution profiles from multimedia testing is not emphasized for IR products for generics Dissolution testing in 3 media covering the pH 1.2-6.8 is recommended if there is pH-dependent dissolution for new drugs	Dissolution testing should be performed in 3 media covering the pH 1.2-6.8 and in the quality control (QC) medium (if different from the three media)
Use of surfactant is acceptable, if justified and optimized	Use of surfactant is allowed only in the QC media if justified and supported by method development

* -Dissolution Testing of Immediate Release Solid Oral Dosage Forms (August 1997);
-Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances (August 2018)
**Bioavailability Studies Submitted in NDAs or INDs - General Considerations (April 2022)

Presumed Impact: Medium

Major Differences —3
(Assessment of Dissolution Profile Similarity, Section 2.4)

Profile similarity using similarity factor f2 or bootstrapped f2

- Improves upon the metric to be used to assess the variability of the data and establishes SD >8% as the variability threshold beyond which use of f2 is not appropriate

- Revises the criterion for the lower bound of the 90% bootstrapped CI to ≥ 46 and recommends mean of bootstrap f2 ≥ 50

SD: standard deviation; CI: confidence interval

Recap of General Restrictions of f2 Test

- Dissolution profiles should include at least time 3 but no more than 6 timepoints (3-4 points ideal; zero excluded]
- Only one measurement should be considered after 85% dissolution of either products
- Using f2 is not appropriate when variability exceeds certain thresholds
  - ICH M9 (BCS Waiver): NMT 20% CV up to 10 minutes and NMT 10% CV at later timepoints
  - IR Dissolution Testing Guidance (Aug 1997): NMT 20% CV at the earlier time points (e.g., 15 minutes) and NMT 10% CV at other timepoints

Dissolution Similarity

FDA Guidance on Dissolution and Current Practice*	Draft ICH M13B (Section 2.4)
Similarity test based on f2 or Bootf2 is applied only if ≥ 85% of drug release is achieved (complete dissolution) Similarity is assumed and f2 test is not applied if ≥ 85% of drug is released within 15 minutes (very rapid dissolution)	Similarity test based on f2 or Bootf2 should be applied even if the dissolution in compendial buffers is incomplete (< 85% of drug release is achieved) Similarity is assumed and f2 test is not applied only if ≤ 10% or ≥ 85% of drug is released within 15 minutes
In practice, Bootf2 is mainly used when data exceed the variability (CV%) threshold	Bootf2 is recommended when SD is > 8% at any timepoint, for either strengths
The criterion for the lower bound of the 90% Bootf2 CI ($F2\_5^{th}$) is **≥ 50***	The criterion for the lower bound of the 90% Bootf2 CI ($F2\_5^{th}$) is **≥ 46** and the point estimate (Bootf2) should be ≥ 50

Bootf2: bootstrapped f2

Presumed Impact:
High (similarity to be determined from all media)

Refining the Measure of Variability for f2 - SD vs. CV

SD is a better measure of variability for the mean of the dissolution data

- The variability measures for both CVs and SD are arbitrarily set, however SD involves less variables (n=1) compared to CV (n=3-4)
- SD is independent of the mean and eliminates the need to define “early” and “late” timepoints, and the 2 different CVs (20% and 10%)

<u>Establishing an equivalent threshold criterion for SD</u>

The cut-off of SD > 8% for switching from f2 to bootstrapped f2 (Bootf2) was established, based on:

- Simulation study that showed 6-8% SD was reasonable to replace the CV criteria. The underlying assumptions for the simulations were based on the expected drug release for the dissolution profiles of oral IR drug products
- Review of 105 dissolution datasets showed that
  - using 8% SD to replace the current CV criteria showed matching frequency of switching

CV: coefficient of variation

Presumed Impact: Low

f2 by 5th Percentile Method-Bootf2

The current criterion for lower bound 90% Bootf2 CI (F2_5th) ≥ 50 is **stricter** than f2 ≥ 50, causing **inconsistency** for concluding profile similarity

- Empirical data for the bio-strengths (R vs. R* data) sometimes show lower bound CI values for Bootf2 < 50
- Similarity test allows f2 values close to 50 to pass but may fail to meet the CI criterion for Bootf2

Lower bound 90% Bootf2 CI ≥ 46 recommended as a reasonably conservative criterion

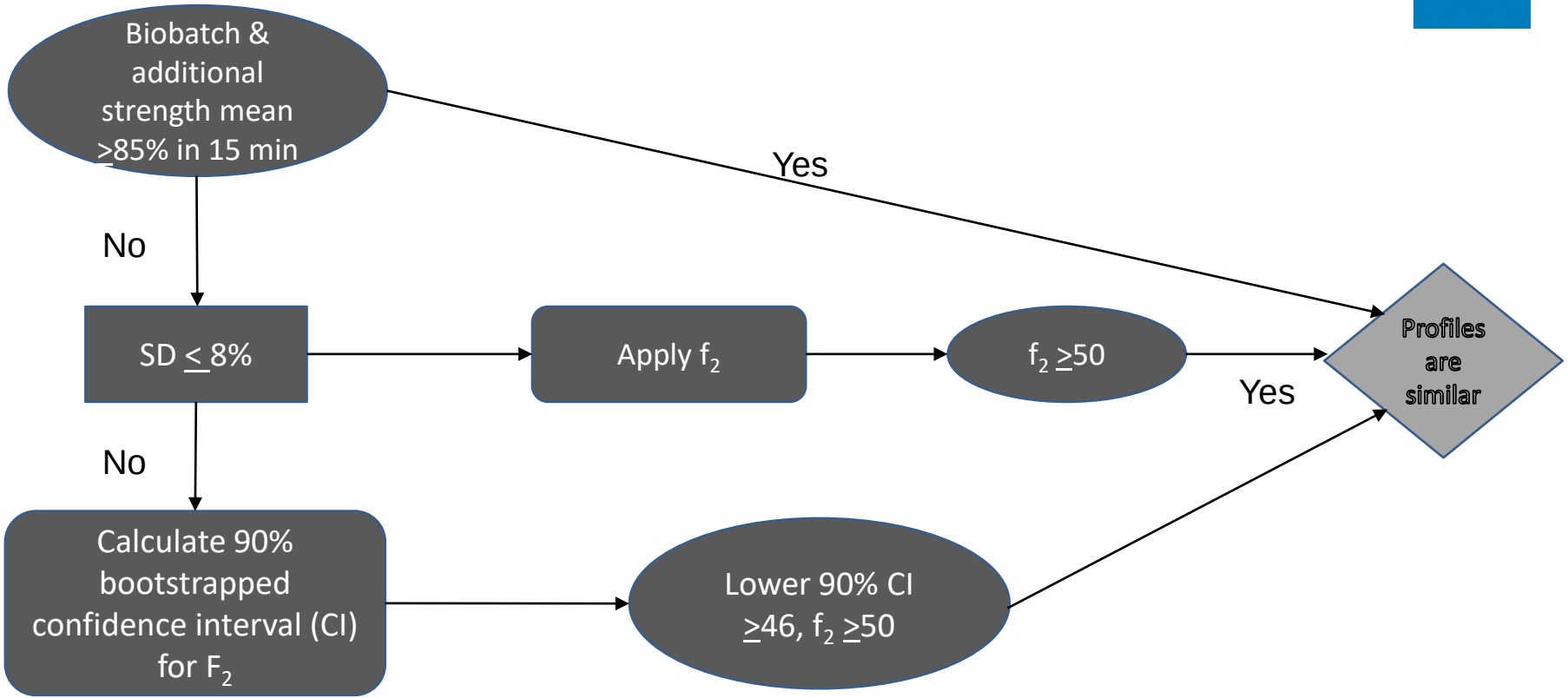
- Results from 2 independent simulation studies showed the lower bound 90% Bootf2 CI **≥ 46** was a reasonably conservative criterion, offered more flexibility than the current criterion and could maintain consistency in results across the 2 similarity tests

Additionally, **mean Bootf2 ≥ 50** is recommended to assure that on average the mean difference at each timepoint on the profiles is within 10%

* R for profile comparisons is the biobatch-strength

Presumed Impact: Low

Decision Tree for Dissolution Profile Similarity



M13B Draft Guidance, Figure 1

Summary of Recommendations in Draft M13B that are not in Draft FDA ANDA PK BE Guidance (Aug 2021)* --Specific Topics

* *Guidance for Industry: Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application (Aug 2021)*

M13B: Specific Topics

1. Fixed dose combination
2. Bracketing approach
3. Drug substance instability
4. *Documentation*

M13B: Specific Topics (1)

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 (Annex I).

- FDC is formulated with the individual drug substances in separate layers, criteria 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) and should be considered independently for each layer.

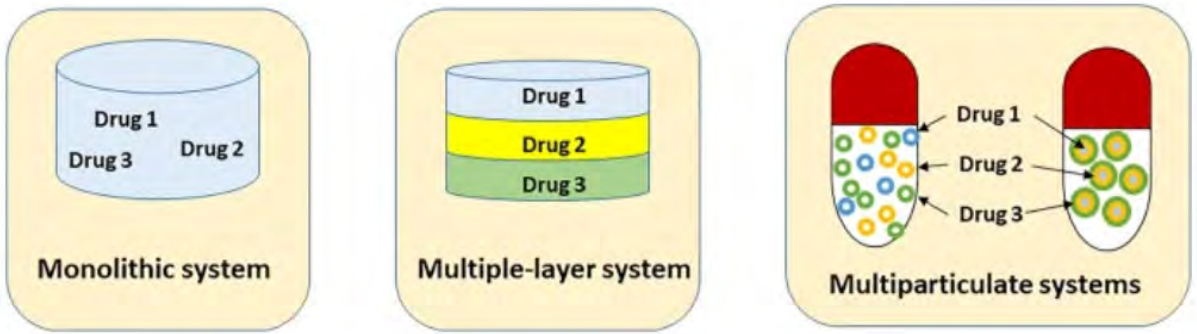
FDC: fixed dose combination product

Fixed Dose Combination Products (3.1)

Not covered in current FDA *Guidance for Industry: Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application (Aug 2021)*

FDC

- Formulation Proportionality considerations dependent on formulation design.



Types of FDC systems, including monolithic, multiple-layer, and multiparticulate systems.

Presumed Impact: Medium

M13B: Specific Topics (2)

3.2 Bracketing Approach

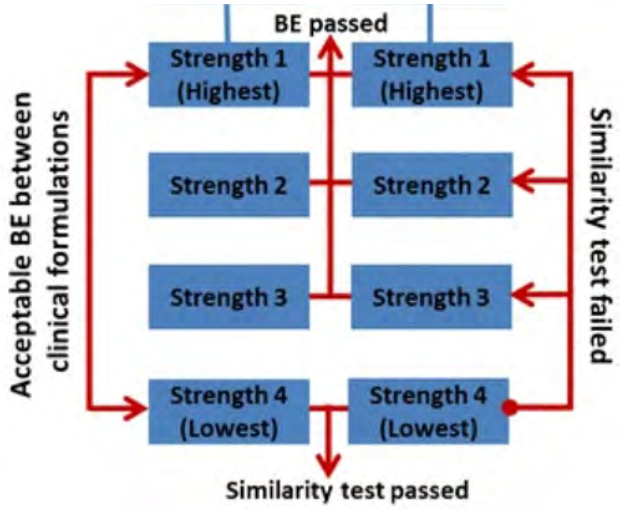
- Assuming qualitative similarity is maintained between strengths, a bracketing approach may be used when BE assessment at more than two strengths is needed

Bracketing Approach (3.2)

Bracketing approach

- Dissolution dissimilarity between strengths
- Deviations from direct proportionality in core composition exceeding those described in Annex I
- Non-dose proportional PK

Presumed Impact:
Low



Fixed Dose Combination Products (3.1)

Component	Function	Strength (label claim)								
		40 mg/20 mg		40 mg/15mg		40 mg/10mg		40 mg/5 mg		
										Absolute % difference relative to core weight of lowest strength compared to highest strength
		Quantity per unit		Quantity per unit		Quantity per unit		Quantity per unit		
		mg	%*	mg	%*	mg	%*	mg	%*	
Drug A	Active ingredient	40.0	10.0	40.0	10.0	40.0	10.0	40.0	10.0	--
Drug B	Active ingredient	20.0	5.0	15.0	3.8	10.0	2.5	5.0	1.2	--
Lactose monohydrate	Diluent/filler	320.0	80.0	325.0	81.2	334.0	83.5	339.0	84.8	4.8
Pregelatinised starch	Binder	10.0	2.5	10.0	2.5	10.0	2.5	10.0	2.5	0.0
Magnesium stearate	Lubricant	10.0	2.5	10.0	2.5	6.0	1.5	6.0	1.5	1.0
Total		400.0	100.0	400.0	100.0	400.0	100.0	400.0	100.0	
Total absolute value of excipient changes (%)										5.8
Total absolute value of deviation in total core weight of additional strength (%) from theoretical directly proportional version considering Drug A			--		0.0		0.0		0.0	

*each ingredient expressed as a percentage of the total core weight

Presumed Impact:
Medium to High

Draft M13B Guidance, Annex I Example 4

M13B: Specific Topics (3)

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 (Annex), applicants can justify time-dependent high solubility.

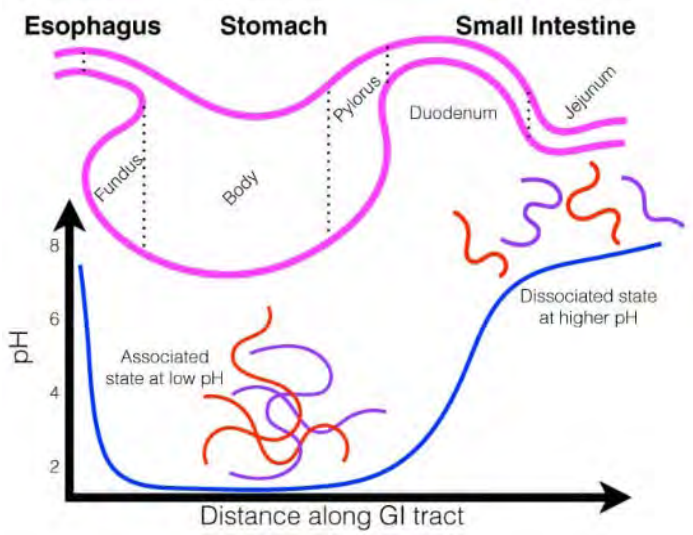
Presumed Impact: Low

M13B: Drug Substance Instability

3.3 Drug Substance Instability

Additional data to justify time-dependent high solubility include concentration vs. time measurements for the drug substance and any degradation products of the drug substance for the same duration as for the dissolution experiment.

If sufficient information cannot be provided to demonstrate time-dependent high solubility, the drug substance should be considered low solubility within this context.



New Material Could Improve Gastrointestinal Drug Delivery of Medicines | BenchChem

M13B: Documentation

4 Documentation

To support a biowaiver request, a comprehensive documentation (Biowaiver Report) should be provided. This report should include:

- A tabular listing of the biobatch strength(s) and the additional strength(s) with their qualitative and qualitative compositions, excipient quantity per unit, and quantity of each ingredient as a percentage of the total core weight. **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 assessment.
- Conclusion providing sufficient evidence to support the bioequivalence of the additional strength(s).

Presumed Impact: Low

Summary

- There are areas of changes from FDA's current practice in M13B for harmonization across regulatory agencies
- Draft M13B guidance has been under public consultation to collect comments
- You may submit your comments to the FDA via the docket: FDA-2023-D-0093 by **October 9, 2025**
- ICH M13B expert working group will review and discuss comments
  - Q and A may be developed based on comments received to provide additional clarity to assist implementation

Resources

- FDA Draft Guidance: M13B Bioequivalence for Immediate-Release Solid Oral Dosage Forms: Additional Strengths Biowaiver (May 2025)
- ICH M13B Step 2 Presentation (March 2025)
- FDA Final Guidance: M13A Bioequivalence for Immediate-Release Solid Oral Dosage Forms (Oct 2024)
- FDA Draft Guidance: Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application (August 2021)
- FDA Draft Guidance: Statistical Approaches to Establishing Bioequivalence (December 2022)
- FDA Office of Generic Drugs Global Generic Drug Affairs
- Product-Specific Guidances for Generic Drug Development (main page)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