ICH M13 Guideline Series

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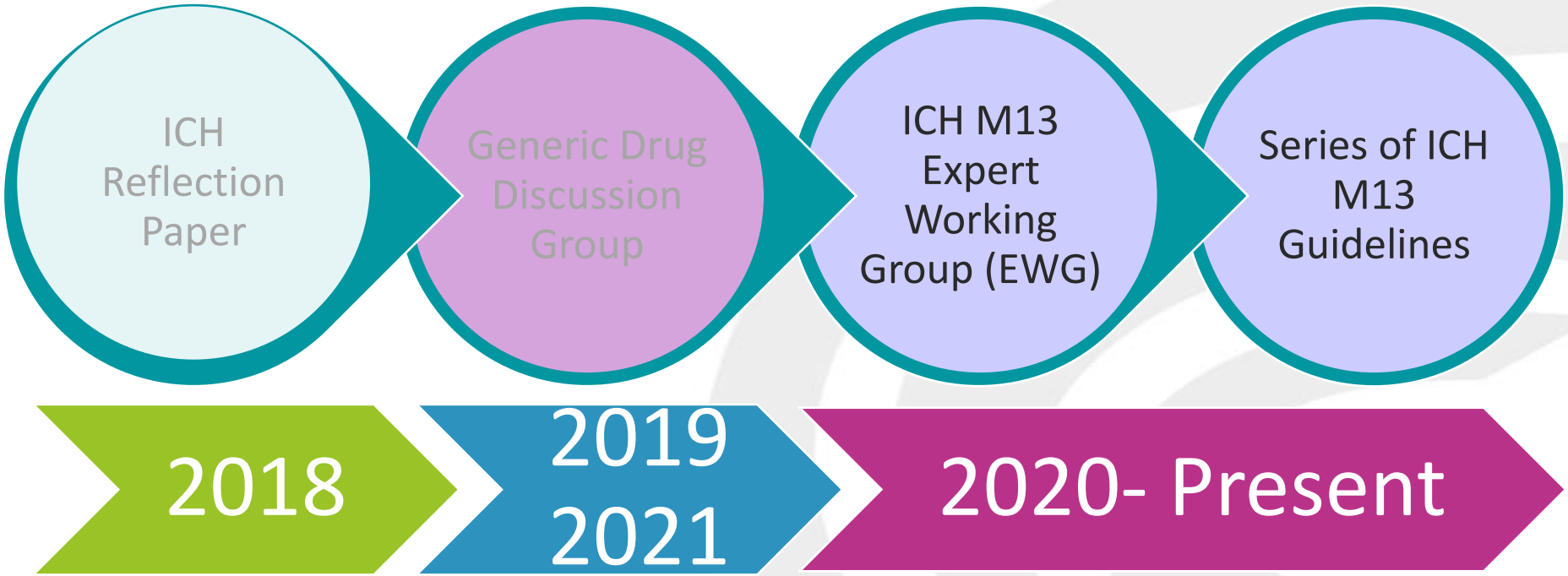
Current: Member of ICH M13 EWG and ICH Generic Discussion Group

Past: Member of the ICH M9 EWG

Background (1)

- Generic medicines comprise a significant portion of the pharmaceutical market
- Bioequivalence (BE) assessment is important for establishing therapeutic equivalence for generic medicines to their respective comparator products
- ICH Reflection Paper on *"Further Opportunities for Harmonisation of Standards for Generic Drugs"* (endorsed by ICH in Nov 2018): 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

Background (2)



M13 EWG:

Rapporteur: Lei Zhang, FDA, US
Regulatory Chair: Jan Welink, EC, Europe
Rapporteur Supporter: Debbie Cordaro, FDA, US

M13 Member Parties

ANVISA, Brazil
EC, Europe
EFPIA
FDA, US
GSCF
HSA, Singapore
Health Canada
IFPMA
IGBA
JFDA, Jordan
JPMA
MFDS, South Korea
MHLW/PMDA, Japan
NMPA, China
PhRMA
Swissmedic, Switzerland
TFDA, Chinese Taipei
TGA, Australia
WHO
MHRA, UK (04/2023)
SAHPRA, South Africa (06/2023)

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M13 Objectives (1)

- Focus on **immediate-release (IR) solid oral dosage forms** designed to deliver drugs to the systemic circulation. For example,
  - Tablets
  - Capsules
  - Granules/powders for oral suspension
- Provide recommendations on conducting BE studies during:
  - Product development
  - Post-approval phases

M13 Objectives (2)

- Harmonize current regional guidelines/guidances
- Reduce need to conduct multiple BE studies for multiple jurisdictions
  - Reduce the need for multiple different sets of data and information from duplicative BE studies
- Support streamlined global drug development

Scope and Organization of M13 (1)

M13 guideline development includes three tiers:

- **Tier 1 → M13A:** First guideline in the series
  - Scientific / technical aspects of study design and data analysis to support BE assessment
  - How regulatory decisions are made based on the BE assessment is out of scope
  - Acceptance of comparator products across regulatory jurisdictions
    - Could reduce burden of multiple clinical trials
    - Governed by local laws therefore out of scope

Scope and Organization of M13 (2)

- **Tier 2 → M13B**: Second guideline in the series
  - BE for additional strengths of a product line including biowaiver considerations
    - BE study(ies) conducted with one strength (bio-strength)
    - Relationship to bio-strength
    - Biowaiver from requirement for additional studies
      - Dose proportionality in the pharmacokinetics of the comparator product
      - Qualitative and quantitative composition comparison among strengths
      - Comparative in vitro dissolution
      - Assessment of similarity between dissolution profiles

Scope and Organization of M13 (3)

- **Tier 3 → M13C**: Third guideline in the series
  - BE study design, analysis, and assessment for
    - Highly variable drugs
    - Drugs with narrow therapeutic index (NTI)
    - Complex BE study design and analysis considerations

M13 Progress

M13A

- Start: Jul 2020
- *Step 1*: Dec 9, 2022
- *Step 2*: Dec 20, 2022
- **Current Status:** *Step 3* Public Consultation

M13B

- Start: Nov 2022
- **Current Status:** Draft technical document under development towards consensus

M13C

- Start: After M13B *Step 2*

ICH Process of Harmonization

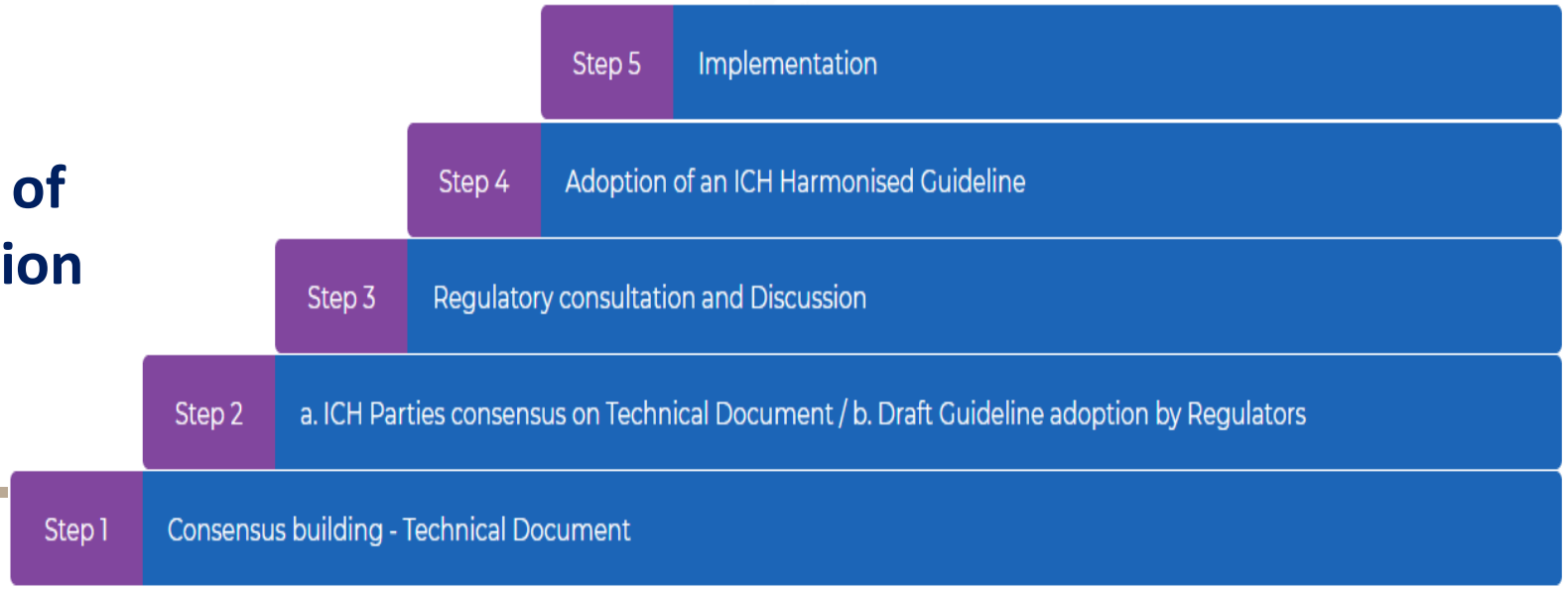


Table of Content of M13A Guideline (1)

- **1. Introduction**
  - 1.1 Objective
  - 1.2 Background
  - 1.3 Scope
- **2. General Principles in Establishing Bioequivalence**
  - 2.1 Study Design for Pharmacokinetic Endpoint Bioequivalence Studies
  - 2.2 Data Analysis for Non-Replicate Study Design

Table of Content of M13A Guideline (2)

- **3. Specific Topics**
  - 3.1 Endogenous Compounds
  - 3.2 Other Immediate-Release Dosage Forms
  - 3.3 Fixed Dose Combination
  - 3.4 pH-Dependency
- **4. Documentation**
- **5. Glossary**

M13A: Introduction (1)

- BE assessment is important in:
  - Therapeutic equivalence for generic drug products vs. comparator products
  - New (originator) drug development when demonstration of BE may be critical for approval decisions
  - BE studies are used by originator and generic product developers to support post-approval formulation and/or manufacturing process changes
- The Biopharmaceutics Classification System (BCS)-based biowaiver may be used to waive in vivo BE studies for certain orally administered IR solid oral dosage forms (ICH M9, *Biopharmaceutics Classification System-Based Biowaivers)*
- Deviations from the recommendations in guidelines may be acceptable if appropriate scientific justification is provided
- Applicants are encouraged to consult the regulatory authority(ies) when an alternate approach is proposed or taken

M13A: Introduction (2)

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

  Public consultation (EMA) ongoing

- The pharmacokinetic (PK) principles of this guideline are generally applicable to non-orally administered drug products with immediate action in which reliance on systemic exposure measures is suitable for establishing BE, e.g., certain rectal, inhalation, and nasal drug products

M13A: Introduction (3)

Out of scope:

- Acceptance of comparator products across regions
- BE for additional strengths → M13B
- BE for highly variable drugs and NTI drugs → M13C
- PK study design or data analysis to support bioavailability (BA) assessment for new drug development in support of intended use or dosing recommendations in drug labeling, e.g., relative BA, food effect, drug-drug interactions, etc.

M13A: Study Design (1)

- Study Population
  - Normally healthy subjects
- Study Design
  - Normally a randomised, single-dose, two-period, two-sequence crossover study design
    - For safety/tolerability reasons, possibly single-dose or multiple-dose study in patients
    - For drugs with a long elimination half-life: parallel design
- Sample Size

M13A: Study Design (2)

- **Test Product**
  - Representative of product to be marketed
- **Comparator Product**
  - Product accepted by regulatory authorities that can be compared against the Test Product in BE study

M13A: Study Design (3) – Fasting and/or Fed Conditions

- 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
  - The properties of drug substance
  - The properties of the products being compared (“non-high risk” or “high risk”)

M13A: Study Design (4) – Fasting and/or Fed Conditions

Non-high Risk Products:

- Fasting BE: where the labeling indicates intake only under fasting or under fasting or fed conditions
- Fed BE: where the labeling indicates intake only under fed conditions, due to a pharmacokinetic (PK) reason
- Fasting or fed BE: where the labeling indicates intake only under fed conditions, due to tolerability reasons

High Risk Products

- Both fasting and fed conditions, irrespective of the product labeling with regard to food intake, except when safety concerns make it unethical

M13A: Study Design (5)

Dose or Strength to be Studied

Dependent on the pharmacokinetics (PK) and solubility of the drug

- Dose proportional PK: in general, the highest strength should be administered
- More than dose proportional increase in PK: highest strength
- Less than dose proportional increase in PK:
  - If due to saturation of absorption: lowest strength
  - If due to solubility or unknown reason: lowest and highest strength

M13A: Study Design (6)

- Moieties to be Measured
  - Parent vs. metabolite
  - Enantiomers vs. racemates
- Sampling
  - Blood sampling scheme
  - First point C_{max}
  - Long half-life drugs
  - Early exposure

M13A: Data Analysis (1)

- Single-dose PK parameters should be tabulated:
  - Primary parameters: $AUC_{(0-t)}$(or $AUC_{(0-72h)}$), $C_{max,}$ and pAUC, where applicable
  - Additional parameters: $AUC_{(0-inf)}$, $AUC_{(0-t)}/AUC_{(0-inf)}$, T_{max}, k_{el}, $t_{1/2}$
  - $AUC_{(0-t)}$ should cover at least 80% of $AUC_{(0-inf)}$, except in case AUC is measured over 72 hours
- Standard statistical approaches should be employed
  - Non-replicate study
- 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%

M13A: Data Analysis (2)

- Studies where **multiple Comparator Products** are included
  - Multiplicity correction, i.e., alpha adjustment, is not needed, because Comparator Products are considered independent and region-specific

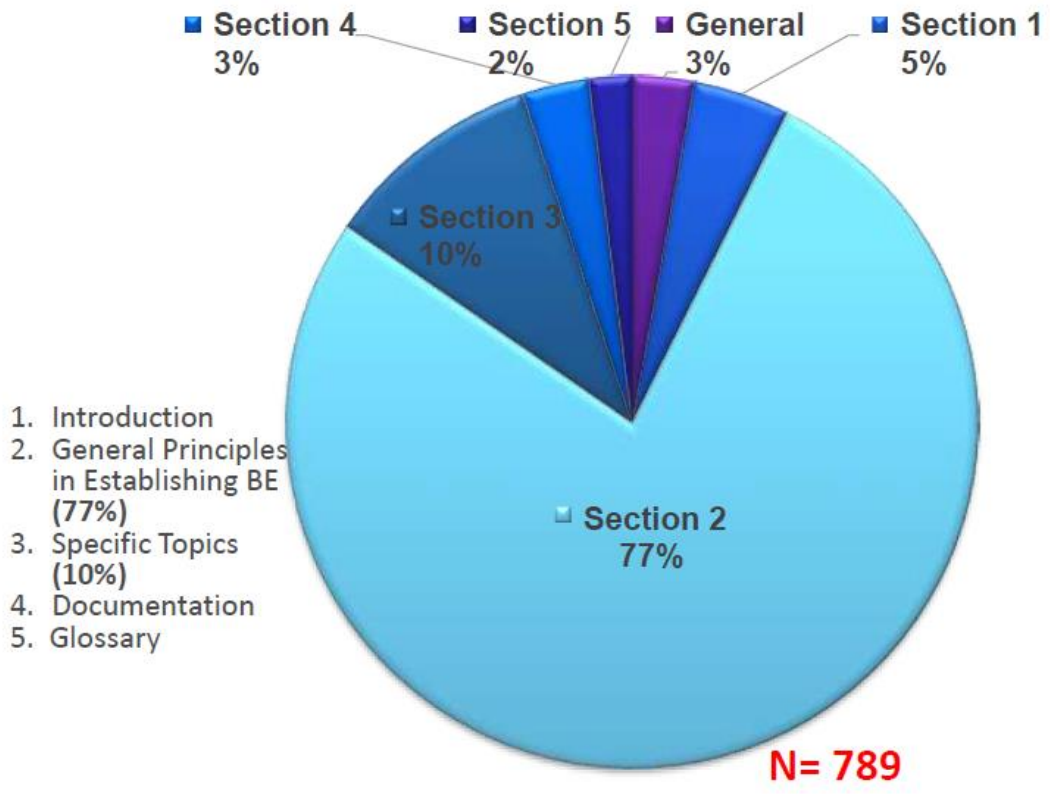
- Studies where **multiple Test Products** are included
  - Application of multiplicity correction depends on the underlying objectives of the study

M13A: Specific Topics (1)

- Endogenous compounds
- Other IR dosage forms
  - Orally Disintegrating Tablets (ODTs)
  - Chewable Tablets
  - Oral Suspensions
- Fixed Dose Combination (FDC) Products
- pH-Dependency

M13A comments

- M13A public consultation period ended
- EWG members are reviewing comments, which will be addressed through consensus and will revise guideline to support finalization



"…the proposed guidance is excellent. It is clearly written, scientifically sound, and overall an important step towards promoting harmonisation of global drug development"

Develop Q&A document to provide details and clarification for the scientific thinking for some recommendations

Develop training materials to facilitate regional implementation and ensure consistency

See more on this

- **Nilufer Tampal @ SBIA 2023—Advancing Generic Drug Development: Translating Science to Approval**

Supporting the First Harmonized Bioequivalence

Guideline Under ICH: Considerations for Future Implementation

Recent developments

Work continues to advance on two fronts:

- Processing of comments received from the M13A public consultation via the various regions

  An example: comments submitted to EMA

- M13: Continuing consensus building and initial drafting effort on M13B
- Upcoming ICH meetings: Prague 2023

Other relevant developments

- ICH General Assembly has adopted a new topic:

"Bioequivalence for Modified-Release Products": new ICH Multidisciplinary Guideline

Important next step for harmonization of bioequivalence standards for more complex dosage forms.

Several elements being harmonized under the M13 series, may be transferrable to this new guideline.

Summary

- The M13 guideline development includes three series: M13A, M13B and M13C
- The harmonized M13 guidelines provide important recommendations on:
  - BE study design
  - Principles for conducting BE studies
  - BE standards for IR solid oral dosage forms
- The draft M13A guideline is under public consultation and comments received will be considered by the M13 EWG while finalizing the guideline
- Additionally, the harmonization process continues with the development of M13B and M13C guidelines
- Implementation of the M13 guideline series will reduce the need for additional *in vivo* BE studies and supports streamlined global drug development.
- This will ultimately benefit patients by increasing access to affordable generic drugs

Acknowledgments

- Lei Zhang – US FDA– Rapporteur of M13
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- Nilufer Tampal – US FDA – EWG member
- M13 Expert Working Group