U.S. FOOD & DRUG ADMINISTRATION

ICH M13 Guideline Series

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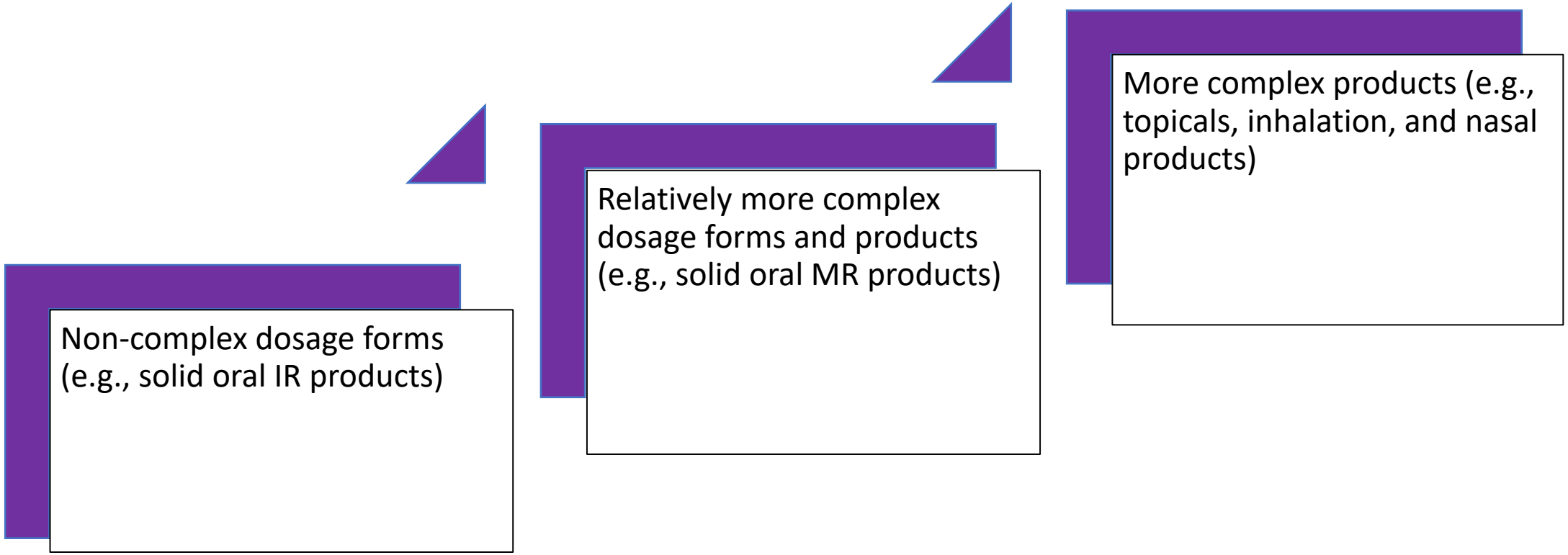
Background

- 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
- Common standards for global development for generics can improve access to generic medicines
- 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

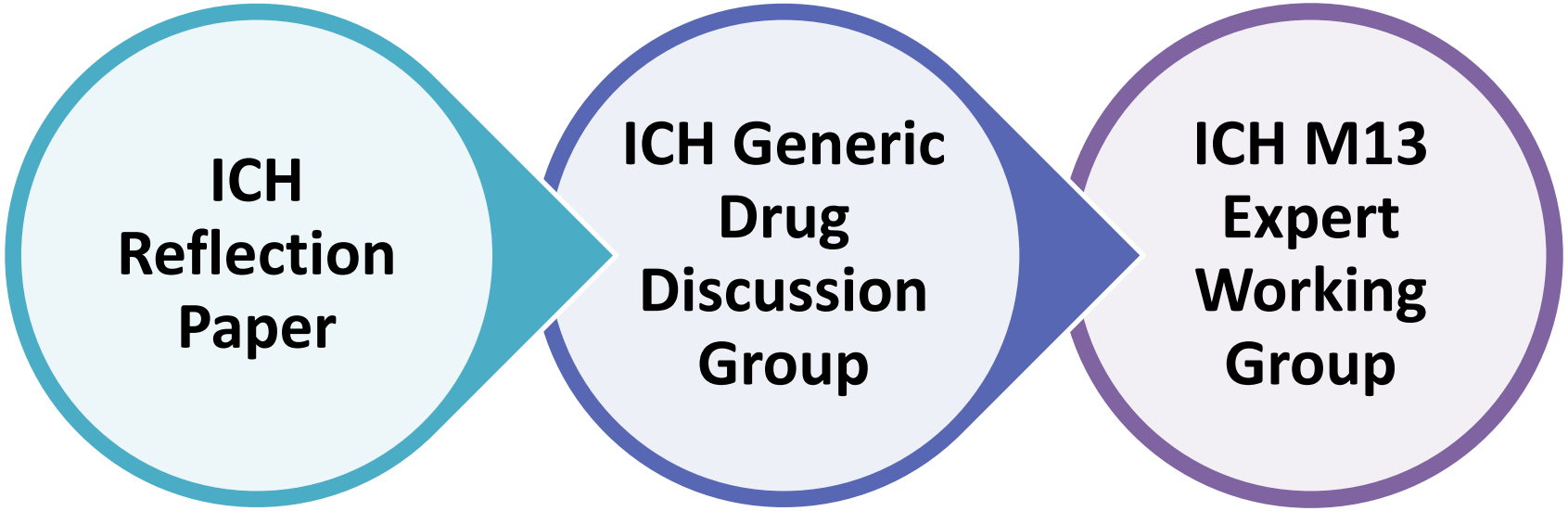
Strategic Roadmap for Harmonized Guidelines for Generic Drugs

- **ICH Reflection Paper on "*Further Opportunities for Harmonisation of Standards for Generic Drugs*"** (endorsed by ICH in Nov 2018)



ICH: The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; IR: immediate-release; MR: modified-release

Progression Towards the First ICH BE Guideline



Nov. 2018

www.ich.org

2019-2020

- Recommended topics for harmonization
- Recommended an order for prioritization
- Supported submission of new topic proposals to ICH **(IR and MR)**

2020 - Present

- BE for IR solid oral dosage forms
- Develop M13 in 3 series

IR: Immediate-Release
MR: Modified-Release

ICH M13 Expert Working Group (EWG)

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

Parties in the Expert Working Group (22)

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

June 2024, Fukuoka Meeting

M13 Objectives (1)

M13 represents the first ICH guideline that focuses on harmonization of BE standards for generic drugs

- Focus on **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 (series):

- **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 (biobatch strength)
    - Relationship to biobatch strength
    - Biowaiver for additional strength(s)
      - 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 Guideline Series and Timeline

M13A

- Start: Jul 2020
- *Step 1*: Dec 9, 2022
- *Step 2*: Dec 20, 2022
- Step 4: July 23, 2024
- **Current Status:** *Step 5;* Ready for regulatory implementation

M13B

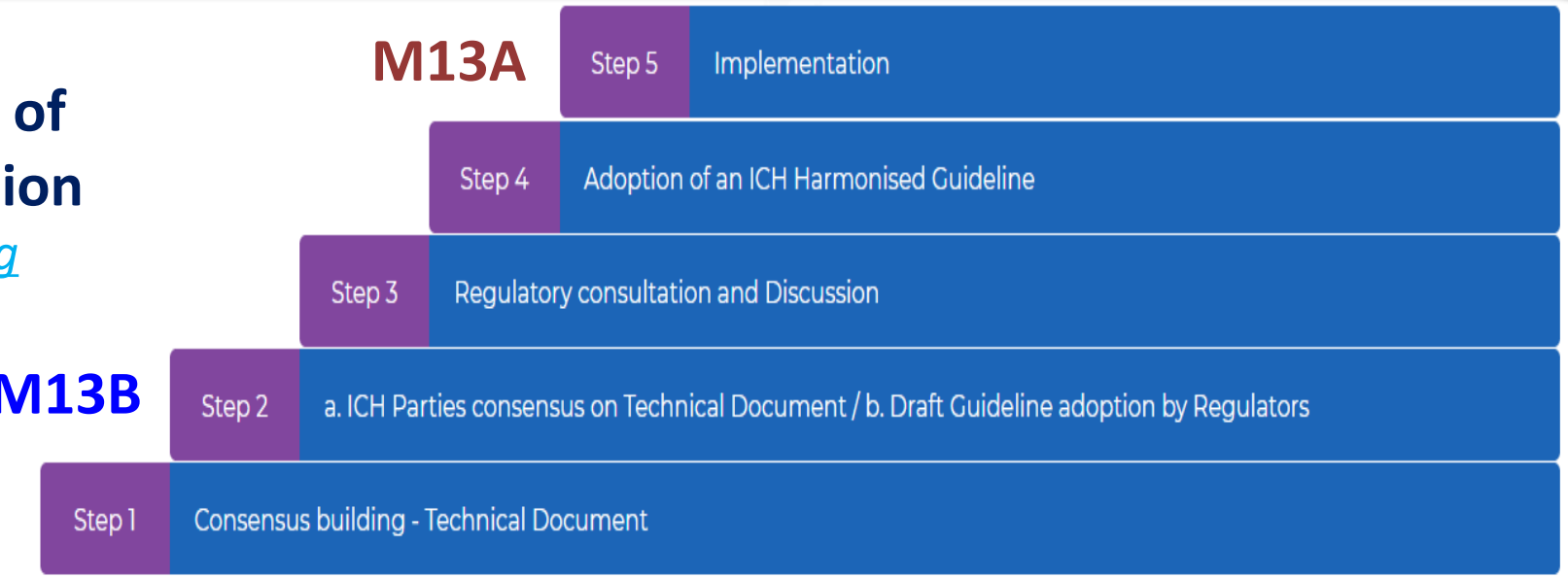
- Start: Nov 2022
- *Step 1:* Feb 12, 2025
- **Current Status:** *Step 2 (est.)*: Feb/March 2025

M13C

- Start: Feb 2025

ICH Process of Harmonization

www.ich.org



ICH Endorsed M13A Final Guideline and its Q&A (July 2024)

ICH harmonisation for better health

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

BIOEQUIVALENCE FOR IMMEDIATE-RELEASE SOLID ORAL DOSAGE FORMS

M13A

Final version

Adopted on 23 July 2024

ICH harmonisation for better health

M13 Expert Working Group

ICH M13A Guideline:

BIOEQUIVALENCE FOR IMMEDIATE-RELEASE SOLID ORAL DOSAGE FORMS

Questions and Answers

M13A Q&As

Adopted on 23 July 2024

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

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Section 2: 11 Q&A
Section 3: 7 Q&A
Section 4: 1 Q&A

https://database.ich.org/sites/default/files/ICH_M13A_Step4_Final_Guideline_2024_0723.pdf
https://database.ich.org/sites/default/files/ICH_M13A_Step4_QAs_2024_0723.pdf

M13A Implementation Status
(As of February 24, 2025)

- **ANMAT, Argentina** - Not yet implemented;
- **ANVISA, Brazil** - Not yet implemented;
- **COFEPRIS, Mexico** - Not yet implemented;
- **EC, Europe** - Not yet implemented; Date: 25 January 2025; Reference: EMA/CHMP/ICH/953493/2022
- **EDA, Egypt** - Not yet implemented;
- **FDA, United States** - Implemented; Date: 31 October 2024; Reference: 89 FR 86809
- **HSA, Singapore** - Not yet implemented;
- **Health Canada, Canada** - In the process of implementation;
- **JFDA, Jordan** - Not yet implemented;

MFDS, Republic of Korea - Not yet implemented;

MHLW/PMDA, Japan - Not yet implemented;

MHRA, UK - Implemented; Date: 1 January 2025;

NMPA, China - In the process of implementation;

SFDA, Saudi Arabia - Not yet implemented;

Swissmedic, Switzerland - Implemented; Date: 23 July 2024; Reference: ICH Guidelines apply in Switzerland automatically upon reaching Step 4: Swissmedic Journal 05/2006, p. 504

TFDA, Chinese Taipei - Not yet implemented;

TITCK, Türkiye - Not yet implemented;

M13B

- Title: "Bioequivalence for Immediate-Release Solid Oral Dosage Forms: Additional Strength Biowaiver"
- Current status:
  - *Step 1*: Feb 12, 2025
  - *Step 2* (est.): Feb-Mar 2025
  - Public commentary period (varies in different regions) (est.): Mar-Sept 2025

M13B Draft Guideline

- Data to support BE for additional strengths of a product line
  - BE study(ies) conducted with one (biobatch) strength
  - Relationship to biobatch strength
  - Biowaiver for additional strength(s)
- Criteria for biowaiver of additional strengths
  - PK dose proportionality of the drug
  - Qualitative and quantitative composition among different strengths
  - Dissolution conditions
  - Similarity assessment of dissolution profiles

M13C

- Supplement to M13 Concept Paper
  - BE study design, analysis, and assessment for
    - Highly variable drugs
    - Drugs with narrow therapeutic index (NTI)
  - Complex study design and analysis considerations

- Work began in Feb 2025

Summary

- The ICH M13 guideline development includes three series: M13A, M13B and M13C
- ICH M13A, the first harmonized ICH guideline in the series that focuses on BE, has been finalized, adopted by ICH, and is ready for implementation by ICH regulatory members, including FDA and other global regulatory agencies (in *Step 5*)
  - Impacts a significant portion of the pharmaceutical market
  - Reduces the need for additional in vivo BE studies due to divergent regulatory recommendations prior to harmonization
  - Supports streamlined global drug development
  - Benefits patients by increasing access to generic drugs
- The process of harmonization continues with M13B and M13C
- Draft M13B guideline will be released for public comments in February to March 2025
- Work on M13C began in February 2025

Acknowledgements: M13 EWG Members

M13A, Fukuoka, June 2024

M13B, Montreal, November 2024

Reference

- SBIA Webinar: “M13A: Bioequivalence for Immediate-Release Solid Oral Dosage Forms - Implementing the Final Guidance” (November 21, 2024): https://www.fda.gov/drugs/news-events-human-drugs/m13a-bioequivalence-immediate-release-solid-oral-dosage-forms-implementing-final-guidance-11212024

Additional Slides

FDA's Implementation and Alignment Efforts (1)

- FDA published final M13A guidance in Oct 2024 following ICH adoption of final M13A guideline in July 2024
- FDA revised >800 oral IR product PSGs to align with M13A
  - 814 revised PSGs posted in Oct 2024
    - Primary focus - Assess risk evaluation for "High-Risk" and "Non-High-Risk" oral IR drug products
    - The most significant change to PSGs (i.e., two BE studies to one BE study)
  - Additional PSGs to align with M13A are being posted in quarterly batches (e.g., Nov 2024)
  - Reduced the need for additional in vivo BE studies compared to what FDA recommended prior to M13A
  - Supported streamlined global drug development

https://www.fda.gov/drugs/guidances-drugs/upcoming-product-specific-guidances-generic-drug-product-development

FDA's Implementation and Alignment Efforts (2)

- Of more than 1,150 published PSGs of oral IR drug products, ~160 PSGs were excluded from the FDA's initial efforts for PSG revision to align with M13A, if they are
  - Narrow therapeutic index drugs
  - Locally acting drug products
  - Products with PSGs recommending BE studies in patients
  - Products with PSGs recommending only one BE study
- ~150 PSGs of oral IR drug products considered as "High-Risk" products were not revised
  - Continue to recommend two BE studies
  - Solid dispersions; lipid-based formulations (e.g., self-emulsifying drug delivery system); nanotechnologies (e.g., micro/nano-emulsions); gastro-retentive formulation; polymer-based (e.g., functional coating); critical excipients
- This initial revision efforts to align with M13A revised ~72% of FDA's existing PSGs for oral IR products and ~37% of total number of FDA published PSGs

https://www.fda.gov/drugs/guidances-drugs/upcoming-product-specific-guidances-generic-drug-product-development