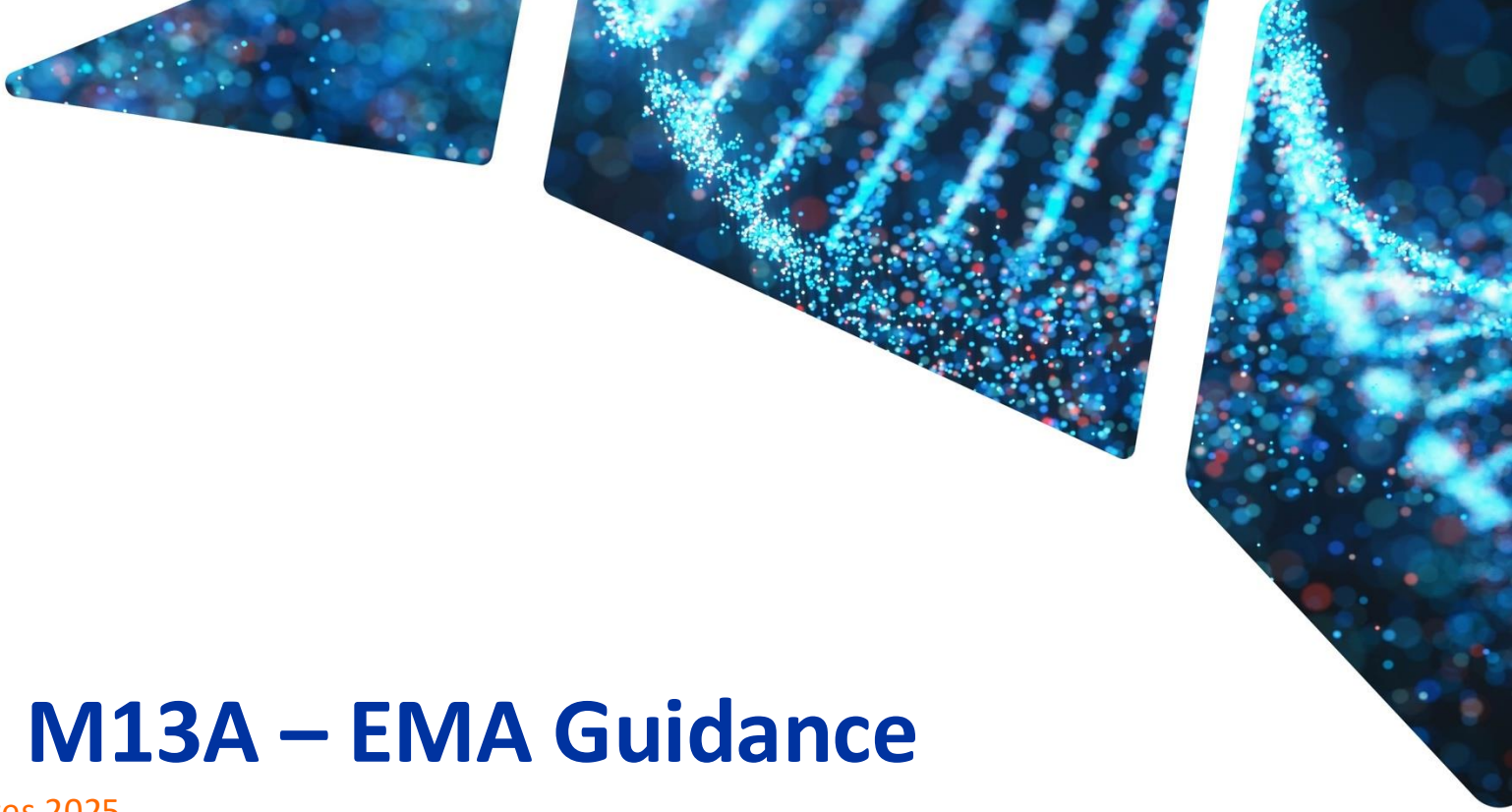

ICH M13A – EMA Guidance

BioBridges 2025

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ICH M13 Guidelines

- M13A guidance
  - Explains study design and data analysis for BE of IR formulations
  - Focuses on PK endpoints
  - Applies to IR oral solid dosage forms
- M13B guidance
  - Recommends conditions under which in vivo BE studies may be waived for one or more strengths, provided BE has been established for at least one strength in the application
- M13C guidance

  Explains study design and data analysis for bioequivalence
  - Highly variable drugs
  - Drugs with narrow therapeutic index

Why ICH M13A

- Global Harmonization
  - Regulatory expectations are aligned across major regions like the US, EU, and Japan
- Consistency In Study Design
  - Clear guidance on how studies should be planned, conducted, and analyzed. This reduces variability and strengthens the reliability of results
- Greater Transparency
  - Making regulatory requirements clearer, which minimizes guesswork and misinterpretation during study planning
- Encourages Best Scientific Practices
  - Promotes robust and standardized methodologies

Why ICH M13A (2)

- Supports Regulatory Convergence for Emerging Markets
  - Offers a harmonized framework that can be adopted by non-ICH countries.
  - Supports regulatory convergence through reliance and mutual recognition pathways.
- Improved Communication Between Stakeholders
  - A common framework enhances dialogue between regulators, sponsors, and CROs
- Encourages Ethical Study Conduct
  - Minimizes unnecessary exposure of healthy volunteers

Practical Challenges with EMA guidelines

Fasting Compliance - Steady State studies

- For multiple-dose, steady-state studies with twice-daily dosing, maintaining ≥14 hours fasting consecutively
  - Examples: Carbamazepine
    - Dosing 8am and 8pm; Fast 2 hrs prior to dosing, Meals 2hrs after dosing
    - After 8pm dosing, 10hrs fasting compliance for the Day 2 morning dose is difficult
    - Requires fasting for ≥14hrs prior to dosing, i.e. daily omission of dinner throughout the study period
    - This prolonged fasting regimen raises potential safety concerns
    - May result in subject withdrawal to protect participants well-being
  - Solution:
    - Use Regulatory Precedents and refer to past EMA cases
    - Update protocol to require 9.5 hours of fasting prior to morning dosing. Mitigates prior safety concerns and improves subject compliance
    - EMA Guidance: Fasting conditions in a multiple dose study needs to be adapted to realistic situations, i.e. morning administration requires a 10-hour fasting interval whereas for all other administrations 4 hour fasting prior to administration is sufficient

Fasting Requirements and Volunteer Safety

Fasting-State Dosing for Higher-Strength Products

- Examples: Ibuprofen (IR) 800 mg
  - Challenge to dosing high doses in fasting state – EMA & FDA
  - Increase GI irritation, nausea, dizziness
  - May lead to subject withdrawals
  - Require on-site medical supervision
- Solution:
  - NSAIDs normally recommended with food by your physician (even SMPC says meal preferred)
  - Pre-screen for tolerability in healthy volunteers
  - Use Regulatory Precedents & Refer to past EMA cases
  - Onsite medical supervision during and post-dosing
  - Justification in protocol - choice of fed-state dosing based on safety data or literature

First Point Cmax

Considerations for Early Cmax Observations

- In certain subject Cmax occurs at the first sampling tp post-dose - rapid absorption
- Now you can exclude the subject from main result & include as supportive data
- Challenges (to conduct not M13A)
  - Excluding these subjects could introduce bias and adversely affect the BE study results
  - Subject sensitive to absorption - Affected by formulation, OTC drugs, food, GI factors
  - Risk of poor sampling - May miss true Cmax
  - Early Tmax can be a concern of dose dumping/safety concerns
  - EMA says up to 20% subjects can have deviation, >20% subject to question
- Solution:
  - Optimize sampling near Tmax - Captures accurate Cmax
  - Use replicate designs - Enables variability estimation for RSABE (Ref. Scale Avg. BE)
  - EMA & FDA – if rapid absorption then include 5min sampling, Cmax and Tmax will delay
  - Pilot study – if 20-30% of subjects have conc. between 30min and 4hr then add 5 or 10min tp

AUC- Widening For Highly Variable Drugs

- EMA regulation- No specific criteria to widen the AUC for highly variable drugs especially oncology oral dosage forms
  - E.g. Sunitinib, Dasatinib, Nilotinib & Ibrutinib exhibit high intra-subject variability – PK incl. AUC
  - Meeting standard BE criteria presents a significant challenge for generic product development

- **FDA**
  - Use of reference-scaled average bioequivalence with AUC criteria is acceptable if the 95% upper confidence bound ≤ 0 and the point estimate falls within 80.00–125.00%

- **Health Canada**
  - BE acceptance limits of AUC can be expanded to 66.7% to 150.0%, provided that the ISCV does not exceed 57.4%
- **EMA**
  - Widening of AUC acceptance limits is not permitted for highly variable or NTI drugs, regardless of variability

- Challenges:
  - Difficult to demonstrate bioequivalence within standard AUC limits.
  - May lead to study failure despite adequate clinical performance
  - Requires larger sample sizes or alternative study designs to mitigate variability
  - Narrow Therapeutic drugs

- Solution:
  - Engage Early with EMA- Scientific advice meetings
  - Variability Data- Robust statistical justification and variability analysis
  - Use Regulatory Precedents- Reference past EMA cases where AUC widening was accepted

Product Specific Guidance Challenges

Product Specific Guidance's (1)

- Revision during or after study completion, creating regulatory uncertainty
  - E.g. Tadalafil & Ibuprofen

- **EMA (June 2023)**
  - 90% confidence interval: 80.00–125.00% for AUC 0-72h and Cmax. Comparable median (≤ 20% difference, 80.00–125.00%) and range for Tmax

- **EMA (June 2025)**
  - 90% confidence interval: 80.00–125.00% for AUC0-72h Cmax, (**and partial AUC**). Comparable median (≤ 20% difference, 80.00–125.00%) and range for Tmax

- Challenges:
  - Revisions may lead to delays, added cost, or need for bridging studies
  - Creates misalignment between study design and current expectations
  - Risk of rejection or request for repeat study
  - Reviewer focuses on latest guidance

- Solution:
  - Regulatory Engagement: Pre-study meetings (e.g., scientific advice) to align on PSG expectations
  - Document Rationale: Document key decisions to justify strategy if PSGs are updated
  - Monitor PSGs: Regularly monitor and assess PSG changes for relevance
  - Align with Updated PSG: Make ready of deviations/ additional analysis data to old PSG

Product Specific Guidance's (2)

- Revision during or after study completion, creating regulatory uncertainty
  - E.g. Trametinib

- **EMA (March 2024)**
  - Study Design: Multiple dose steady state Fasting study
  - Population: Melanoma or non-small cell lung carcinoma patients

- **EMA (Dec 2024)**
  - Study Design: Single dose Fasting study
  - Population: Healthy volunteers

- Challenges:
  - Increases cost burden to generic companies
  - Creates misalignment between study design and current expectations
  - Reviewer focuses on latest guidance

- Solution:
  - Regulatory Engagement: Pre-study meetings (e.g., scientific advice) to finalize the study design

Product Specific Guidance's (3)

- Lacks explicit guidance for complex products/steady-state duration
  - E.g. Niraparib capsules/Brigatinib Tablets

- **FDA**
  - Type of study: PK endpoint, steady-state
  - Study Design: Multiple-dose, two-way crossover in ovarian/NSCLC Cancer patients
  - Strength: Eq. 100 mg (dose = 3x100 mg= 300 mg daily)/180 mg

- **EMA**
  - No guidance published for this molecule & formulation

- Challenges:
  - Inadequate steady-state duration- leads to flawed Cmin/Cmax/AUCτ values
  - Sponsors may make variable assumptions- regulatory scrutiny during assessment
  - Could trigger questions or rejection

- Solution:
  - Conduct PK Simulations: Use PK modeling to estimate time to steady state based on known half-life and accumulation patterns
  - Literature Review: Reference published clinical and PK data to justify duration chosen

Product Specific Guidance's (4)

- Lacks clear guidance on the selection of replicate study designs, particularly for highly variable drugs
  - E.g. Dasatinib & Abiraterone Acetate

FDA	EMA
Applicants may consider using a reference-scaled average bioequivalence approach	PSG does not support replicate design due to lack of data on ISCV. If high variability (CVintra > 30%) is expected, applicants should refer to general guideline recommendations

- Challenges:
  - Impact on Study Planning- Ambiguity may lead to over- or under-powered studies, unnecessary complexity, or redesign
  - Inconsistent Study Designs Across Sponsors- Leads to regulatory unpredictability during assessment and review
- Solution:
  - Literature Review: Assess the study design
  - Regulatory Engagement: Pre-study meetings (e.g., scientific advice) to finalize the study design

Product Specific Guidance's (5)

- Differences in study design and study population among PSGs
  - E.g. Sunitinib, Lapatinib

- **FDA**
  - **Sunitinib**: Multiple dose steady-state study in Cancer patients
  - **Lapatinib**: Single dose fasting study in healthy volunteers

- **EMA**
  - **Sunitinib**: Single dose in healthy volunteers
  - **Lapatinib**: Multiple dose steady state fasting and fed studies in breast cancer patients

- Challenges:
  - Risk of Non-Alignment with EMA Expectations
  - High Regulatory Uncertainty

- Solution:
  - Regulatory Engagement: Pre-study meetings (e.g., scientific advice) to finalize the study design

Metabolites/Enantiomers – YES or NO?

Metabolism & Metabolite Assessment (1)

- Moieties to be measured from ICH M13 *(section 2.1.7 - Parent vs Metabolite)*
  - Case 1: Parent is acceptable
  - Case 2: Metabolite to be measured in case of prodrugs as prodrugs are rapidly eliminated and not able to quantify accurately
  - Case 3: If metabolism through gut wall or gut lumen contributes to efficacy or safety then metabolite to be measured

  - Challenges:
    - CRO or sponsor goes through many literatures to understand the metabolism. In some cases, EMA says only parent and FDA (OGD) says parent and metabolite
  - Solution:
    - Literature Review: Assess the study design

Metabolism & Metabolite Assessment (2)

- Prodrug
  - Examples: Dabigatran
    - EMA PSG - only the Metabolite Dabigatran to be quantified (as dabigatran etexilate is a prodrug and rapidly eliminated)
    - FDA PSG - quantify free (non-conjugated) Dabigatran and Total Dabigatran (non-conjugated plus conjugated dabigatran after complete alkaline cleavage of dabigatran glucuronides) in plasma
  - Challenges:
    - No clarity between ICHM13, EMA and FDA
  - Solution:
    - Need Harmonization

Metabolism & Metabolite Assessment (3)

- Active Metabolite
  - Examples: Fingolimod
    - EMA PSG - only the parent Fingolimod in whole blood to be quantified
    - FDA PSG - quantify Fingolimod and its active metabolite, fingolimod-phosphate, in whole blood
  - Challenges:
    - No clarity between ICHM13, EMA and FDA
  - Solution:
    - Need Harmonization

Enantiomer vs Racemate Assessment (1)

- Moieties to be measured from ICH M13 *(section 2.1.7.2 - Enantiomer vs Racemates)*
  - Case 1: Generally Achiral assay is acceptable
  - Case 2: Quantify the enantiomer if the following conditions are met
    - The enantiomers exhibit different pharmacodynamic properties
    - The enantiomers exhibit different PK properties and
    - The exposure (ACU) ratio of enantiomers is modified by a different in the rate of absorption
  - Case 3: Quantification of only active enantiomer is sufficient in cases where one enantiomer is inactive (or makes low contribution) with respect to both safety and efficacy

  - Challenges:
    - CRO or sponsor goes through many literatures to understand the PK properties of isomers
  - Solution:
    - Literature Review: Assess the study design

Enantiomer vs Racemate Assessment (2)

- Racemic - PSG is Aligned
  - Examples: Ibuprofen (Racemic)
    - 2017 – FDA PSG achiral assay
    - 2017 – EMA PSG chiral assay and BE on S enantiomer
    - 2023 – FDA & EMA both PSG - achiral assay and BE on Ibuprofen 😊 😊 😊
  - Confusion & Uncertainty
    - for EU study in 2023 sponsor did Achiral assay
      - Retained samples to reassay with chiral method later
    - for EU study in 2024 sponsor did Chiral assay - not followed PSG but used SMPC as a guide

Enantiomer vs Racemate Assessment (3)

- Racemic - PSG is Not Aligned
  - Examples: Bicalutamide (Racemic)
    - EMA No guidance
    - FDA recommends achiral assay
  - Confusion & Uncertainty
    - EU study (in 2016 before M13A) – achiral assay done as per sponsor request
    - EMA query – compound undergoes stereo specific metabolism. The S (inactive) isomer is metabolized primarily by glucuronidation. The R (active) isomer also undergoes glucuronidation but is predominantly oxidized to an inactive metabolite followed by glucuronidation. **So, why chiral was not done?**
  - Challenge
    - CRO was asked to respond to query!!!!
    - Not enough sample to re-assay
    - As per current ICH M13 - Chiral assay for Bicalutamide (Two assays to be developed, one EMA one FDA)
  - Conclusion & Solution
    - No clarity between ICHM13, EMA and FDA. Need Harmonization

Certificate of Analysis (COA)

- Sponsor must generate additional COA when the gap between manufacturing and the dosing is more than six months
  - **EMA (Earlier)**
    - No guidance on COA prior to dosing
    - Test & Ref differ by <5%
  - **M13A**
    - Has helped clarify & normalize the process for the better
    - If >6m, Test and Ref could be >5% apart
    - Better quality of product can be used study planning is required
    - Know the exact value before conducting study
    - Health Canada has this requirement

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