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Committee for Human Medicinal Products/ Methodology Working Party

Concept paper on a guideline on investigation of drug interactions in the gastrointestinal tract

Agreed by MWP	20 March 2025
Adopted by CHMP	14 April 2025
Start of public consultation	Not Applicable
End of consultation (deadline for comments)	Not Applicable

The proposed guideline will replace aspects of the Guideline on the investigation of drug interactions (CPMP/EWP/560/95/Rev. 1 Corr. 2**) that are not covered by ICH M12

Comments should be provided using this EUSurvey form. For any technical issues, please contact the EUSurvey Support .

Keywords	Interaction, guideline, food, paediatric formulation, gastric pH, complex formation, enterohepatic recirculation, excipients, absorption

1. Introduction

The ICH M12 Guideline on drug interaction studies came into effect on 30 November 2024, formally superseding the EMA Guideline on the investigation of drug interactions Revision 1 which had been in effect since 1 January 2013. However, ICH M12 does not cover all topics addressed by the EMA Guideline on the investigation of drug interactions. This concept paper proposes a guideline on the investigation of drug interactions in the gastrointestinal tract which are not covered by ICH M12.

2. Problem statement

The ICH M12 guideline focusses on pharmacokinetic drug interactions mediated by metabolic enzymes and drug transporters. However, it does not address drug interactions mediated in the upper gastro-intestinal tract (e.g. due to gastric pH change, formation of complexes or chelates, investigation of food effect). These types of interactions are currently covered by the EMA Guideline on the

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Investigation of Drug Interactions Revision 1, which has been in effect since 1 January 2013. With the planned withdrawal of this guideline, there is a risk of creating a gap in regulatory guidance for the assessment of gastrointestinal drug interactions, an important component of evaluating a new drug's interaction potential. To address this, a dedicated guideline is proposed to provide updated and specific recommendations for investigating gastrointestinal interactions.

3. Discussion (on the problem statement)

An implementation strategy describing the implementation of ICH M12 guideline in the European Union has been published (EMA/460496/2024). The following topics have been identified as related to interactions in the gastrointestinal tract potentially affecting the absorption of an orally administered investigational drug and will be addressed in the new guideline:

- investigation of food effect for new, orally administered medicines
- interactions affecting solubility caused by
    - complex formation
    - changes in gastric pH
    - excipients
- interactions impairing enterohepatic circulation,
- interactions affecting gastric emptying and gastrointestinal motility

4. Recommendation

The MWP and CHMP recommend drafting a guideline on investigation of drug interactions in the gastrointestinal tract. Points that will be addressed are listed in section 3 of this Concept Paper.

5. Proposed timetable

The Concept Paper is not foreseen to be released for external consultation, as it primarily addresses the need to update and replace existing guidance. Instead, the draft guideline, once available, will be consolidated and released for a six-month external consultation period.

6. Resource requirements for preparation

The preparation of the proposed guideline will primarily involve the established drafting group working under MWP (tDG-MWP-ICHM12-QandA).

7. Impact assessment (anticipated)

Since the EMA Guideline on the investigation of drug interactions Revision 1(CPMP/EWP/560/95/Rev. 1 Corr. 2**) is planned to be withdrawn, there would be a lack of guidance on the investigation of gastrointestinal interactions, which is an important aspect of the interaction potential of a new drug. The proposed guideline will ensure continued regulatory clarity and consistency in the assessment of such interactions, building on the principles established in the EMA Guideline on the investigation of drug interactions, while reflecting current scientific and regulatory knowledge. This will benefit both

medicine developers in their clinical pharmacology development as well as regulators involved in the evaluation of new medicinal products.

8. Interested parties

Pharmaceutical industry, contract research organisations, healthcare professionals, academia, regulatory agencies including the FDA and PMDA.

9. References to literature, guidelines, etc.

ICH M12 Guideline on drug interaction studies_Step 5

Guideline on the investigation of drug interactions

Implementation strategy for ICH M12