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Implementation strategy of ICH Guideline M12 on drug interaction studies

Superseding EMA Guideline on the investigation of drug interactions

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Introduction

The purpose of this document is to address specific considerations to enable the practical implementation of [ICH M12 Guideline on drug interaction studies](#) (EMA/CHMP/ICH/652460/2022) in the European Union.

It is intended to provide guidance for Marketing Authorisation Applicants and Marketing Authorisation Holders, Contract Research Organisations, as well as regulators. In addition to new Marketing Authorisation applications, ICH M12 will apply to variations to existing authorised medicinal products.

Background

ICH M12 Guideline on drug interaction studies came into effect on 30 November 2024, formally superseding the previously enforced EMA Guideline on the investigation of drug interactions, Revision 1 of which had been in effect since 1 January 2013. On the date of its coming into effect, applicable stakeholders are required to follow recommendations from the ICH M12 guideline. In addition, existing [EMA Clinical Pharmacology Questions and Answers Section 2 on Drug Interactions](#) will also be superseded by ICH M12.

ICH M12, however, unlike the existing [EMA Guideline on the investigation of drug interactions](#) (CPMP/EWP/560/95/Rev. 1 Corr. 2**), does not address a number of topics to the same extent (see Table 1) as these were considered out of scope in the ICH harmonisation exercise.

Therefore, after 30 November 2024, the existing EMA Guideline on drug interaction studies pertaining to these specific topics will continue to apply until such time as they are replaced by new EMA guidance, anticipated to take the form of Questions and Answers documents.

To address these considerations, this Implementation Strategy has been developed by EMA and is further detailed below.

Implementation Strategy

Table 1. Specific topics not covered by ICH M12 for which the existing EMA guideline will continue to apply:

Topic	EMA Guideline Section/pages
Food effect	5.7.4, Appendices I and IX
Contraceptives	5.3.3.2 p 22
Enterohepatic circulation	5.2.4 p 13
Complex binding	5.1, 5.2.1, 5.3.1
Mass balance study	Appendix V
Interactions affecting solubility, drugs modulating gastrointestinal motility or gastric emptying	5.2.1, 5.3.1
Displacement from protein binding	5.3.2
Special populations, paediatric in particular	5.2.5

Translation into SmPC	5.7
Herbal products	6

[EMA Clinical Pharmacology Questions and Answers](#) that have been addressed in ICH-M12 and will be withdrawn:

- Q and A 2.1, 2.2, 2.3, 2.4, 2.5, 2.6 and 2.7