21 May 2024
EMA/CHMP/ICH/227930/2024
Committee for Medicinal Products for Human Use

ICH M12 Guideline on drug interaction studies

Questions and answers

Transmission to CHMP	21 May 2024
Adoption by CHMP	30 May 2024
Date for coming into effect	30 November 2024

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Document History

Code	History	Date
M12 Q&As	Adoption by the ICH Assembly under *Step 4.*	21 May 2024

References

ICH M12 Drug Interaction Studies

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Preface

In response to questions posted to ICH M12 comment period, several Questions and Answers have been developed to provide clarity around some of the concepts related to evaluation of drug interaction covered in the Guideline.

This Question and Answer (Q&A) document is intended to provide additional clarification and improve harmonization of drug interaction assessment.

The scope and organization of this Q&A document follow that of ICH M12.

1. Introduction

#	Date of approval	Questions	Answers
1.1	May, 2024	With regard to the statement that the results of the mass balance study are generally recommended to be available before starting phase 3 study, please provide more specific recommendations on the timing of mass balance study for DDI evaluation.	The mass balance study is useful for confirming the principal elimination routes of the investigational drug. In this guideline, a general scenario is shown in which strategies for further DDI assessment are considered based on the pharmacokinetic profile of the drug obtained in the mass balance study and *in vitro* studies. Clinical DDI studies can be conducted based on information from *in vitro* studies prior to obtaining additional information from mass balance study. This guideline does not intend to restrict the timing of mass balance study for DDI evaluation, and flexibility should be ensured according to the characteristics of the investigational drug, as mentioned in the text.

2. In Vitro evaluation

#	Date of approval	Questions	Answers
2.1	May, 2024	It is recommended to pool microsomes and hepatocytes from multiple donors for *in vitro* metabolism evaluations (substrate and inhibition evaluations). For what purposes would data from a single donor be acceptable?	In general, it is recommended to pool microsomes and hepatocytes from multiple donors for *in vitro* metabolism evaluations (substrate and inhibition evaluations) in order to have a better representation of expression of the metabolizing enzymes for the entire population. Single donor batches may be used for mechanistic studies (e.g., to evaluate the impact of polymorphisms on the *in vitro* metabolism). Activities of metabolic enzymes of this single batch of hepatocytes or microsomes should be well characterized by using probe substrates.
2.2	May, 2024	Can *in vivo* induction potential always be ruled out when the *in vitro* induction potential of the investigational drug is < 2-fold?	An *in vitro* induction study is considered negative for enzyme induction if the incubations with the investigational drug at the cut-off concentrations or higher give rise to no increase or less than 2-fold increase in mRNA provided that the response of the positive control is ≥ 6-fold. However, some enzymes (e.g., CYP2C8, CYP2C9, CYP2C19 (sometimes CYP2B6)) are less inducible, and the increase in mRNA by the positive control is usually <6-fold. In such a case, the induction potential cannot be ruled out for an investigational drug that increases CYP enzyme mRNA less than 2-fold of the vehicle control but more than 20% of the response of the positive control, along with a concentration-dependent relationship. Example 1 where induction cannot be ruled out: the investigational drug increased mRNA dose dependently but maximal increase of 1.8-fold and the positive control increased mRNA 3-fold, the induction potential of the investigational drug is 40% that of the positive control (40% = (1.8 mRNA fold increase – 1)/(3 mRNA fold increase positive control - 1)*100%). Even though the induction response of the drug is < 2-fold, it is > 20% of the

			response of the positive control; therefore, further evaluation is recommended. Example 2 where induction is unlikely: the investigational drug increased mRNA dose dependently but maximal increase of 1.8-fold and the positive control increased mRNA 5.1-fold, the induction potential of the investigational drug is 19.5% of that of the positive control (19.5% = 1.8 mRNA fold increase – 1)/(5.1 mRNA fold increase positive control - 1)*100%). In this case, no further investigation is needed because the induction response of the drug is < 2-fold, and it is < 20% of the response of the positive control. Therefore, the likelihood of induction *in vivo* is low.
2.3	May, 2024	Why is comparison of polarity between unchanged drug and metabolites not a selection criterium for the metabolite as DDI precipitant?	Metabolites are often more polar than the unchanged drug. However, a recent literature report suggests no clear relationship between the polarity of some metabolites versus parent drug and inhibition potency (Steinbronn et al., 2021 CPT, 110:452-463). Hence, polarity is not included as a selection criterium for the metabolite as a DDI precipitant.
2.4	May, 2024	What are the cut-off values for drugs as precipitant of transporters that are not listed in Table 1?	For the transporters listed in Table 1, cut-off values have been proposed based on *in vitro*-to-*in vivo* extrapolation (IVIVE) analyses; however, no IVIVE criteria has been established for other transporters (e.g., OCT1, MRP2). The organ and the cellular localization of a transporter are important factors for understanding the relevance of inhibitor concentrations at the site of the transporter. Therefore, cut-off values for transporters that are not listed in Table 1 may be deduced from the cut-off values from transporters listed in Table 1 when the similarity in organ and the cellular localization of the transporter are taken into consideration.

3. Clinical evaluation

#	Date of approval	Questions	Answers
3.1	May, 2024	What are the unique considerations regarding DDI evaluations for determining the effect of an investigational drug on contraceptive steroids?	The scientific principles described in ICH M12 are generally applicable for the drug interaction evaluation of the effect of an investigational drug on contraceptive steroids. However, the risk of a DDI with contraceptive steroids for drugs that have teratogenic potential should be considered if the drug is intended for use in women of childbearing potential. For more information, refer to regional guidance where available or contact the relevant regulatory authorities.

4. Reporting and interpreting clinical DDI study results

#	Date of approval	Questions	Answers
4.1	May, 2024	How is the number of subjects determined for DDI studies?	As stated in the guideline, the number of subjects included in a DDI study should be sufficient to provide a reliable estimate of the magnitude and variability of a potential interaction. When determining the sample size, factors to consider include the expected variability, the anticipated magnitude of the interaction, and how the data will be used (e.g., to rule out an interaction, to quantify an interaction, to support a dose adjustment). Typically, a clinical DDI study includes around 12-20 subjects, but larger studies may be needed, for example, when variability is high or based on the specific objectives of the study.

5. Appendix

7.3 In Vitro evaluation of metabolism-based DDIs

#	Date of approval	Questions	Answers
7.1	May, 2024	Why are sponsors encouraged to measure concentrations of the parent drug in the medium on the last day of incubation with hepatocytes for *in vitro* induction studies?	The induction potency might be underestimated when the concentration of the investigational drug is lower in the incubation medium than the nominal concentration. Potential causes for the reduced concentrations should be discussed. For drugs that are extensively metabolized or transported, a lower concentration in the medium can be expected because the drug is taken up by the hepatocytes and/or metabolized. In such a case, a decrease in drug concentration over time is expected. Since this is reflecting the *in vivo* situation, no correction for the lower medium concentration is necessary. Lower concentrations could also be due to instability of the drug in the medium. In such case, a decrease in concentration is also expected to occur in medium without hepatocytes. Correction for instability or more frequent refreshment of the medium should be considered. As for other *in vitro* assays, non-specific binding of the drug to materials or cells and precipitation could also be reasons for a lower unbound concentration of the drug in the medium than the nominal concentration. Especially for highly protein bound drugs, this scenario could be an issue. Sponsors should discuss the potential impact of the discrepancy on data interpretation and correct for these non-metabolism/transporter confounders.

7.2	May, 2024	Why is characterization of drug recovery considered important for *in vitro* experiments?	For *in vitro* experiments, good practices include evaluating the recovery of the investigational drug in the test system and measuring or calculating the unbound investigational drug concentration in the incubation solution. For quantitative objectives such as determination of $K_{i,u}$ or $IC_{50,u}$, a high recovery is desirable. On the other hand, for qualitative purposes (e.g., substrate yes/no), a lower recovery may not preclude a conclusive answer. The nature and extent of the effects leading to a decrease of recovery should be investigated. The following factors should be considered: - (metabolic) stability of the drug for the duration of study; - effect of nonspecific binding of the drug to cells/apparatus; - drug's solubility. The potential impact of the discrepancy on data interpretation should be discussed.