M12 Drug Interaction Studies Questions and Answers

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

August 2024
ICH-Multidisciplinary

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Contains Nonbinding Recommendations

FOREWORD

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) has the mission of achieving greater regulatory harmonization worldwide to ensure that safe, effective, and high-quality medicines are developed, registered, and maintained in the most resource-efficient manner. By harmonizing the regulatory expectations in regions around the world, ICH guidelines have substantially reduced duplicative clinical studies, prevented unnecessary animal studies, standardized safety reporting and marketing application submissions, and contributed to many other improvements in the quality of global drug development and manufacturing and the products available to patients.

ICH is a consensus-driven process that involves technical experts from regulatory authorities and industry parties in detailed technical and science-based harmonization work that results in the development of ICH guidelines. The commitment to consistent adoption of these consensus-based guidelines by regulators around the globe is critical to realizing the benefits of safe, effective, and high-quality medicines for patients as well as for industry. As a Founding Regulatory Member of ICH, the Food and Drug Administration (FDA) plays a major role in the development of each of the ICH guidelines, which FDA then adopts and issues as guidance to industry.

Contains Nonbinding Recommendations

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(PREFACE)

In response to questions posted to the International Council for Harmonisation (ICH) draft guidance for industry *M12 Drug Interaction Studies* comment period, several questions and answers have been developed to provide clarity around some of the concepts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 guidance.

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 the ICH guidance for industry *M12 Drug Interaction Studies* (August 2024) (ICH M12).[2]

[1] This guidance was developed within the Expert Working Group (*Multidisciplinary*) of the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This document has been endorsed by the ICH Assembly at *Step 4* of the ICH process, May 2024. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory bodies of the ICH regions.

[2] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

I. INTRODUCTION (1)[3]

Table 1. Q&A for Section I (1) of ICH M12

Number	Date of Approval	Question	Answer
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 drug-drug interaction (DDI) evaluation.	The mass balance study is useful for confirming the principal elimination routes of the investigational drug. In this guidance, 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 before obtaining additional information from mass balance study. This guidance 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.

[3] The numbers in parentheses reflect the organizational breakdown of the document endorsed by the ICH Assembly at Step 4 of the ICH process, May 2024.

II. IN VITRO EVALUATION (2)

Table 2. Q&A for Section II (2) of ICH M12

Number	Date of Approval	Question	Answer
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 less than 2-fold?	An in vitro induction study is considered negative for enzyme induction if the incubations with the investigational drug at the cutoff 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 greater than or equal to 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 less than 6-fold. In such a case, the induction potential cannot be ruled out for an investigational drug that increases cytochrome P450 (CYP) enzyme mRNA less than 2-fold of the vehicle control but more than 20 percent of the response

Number	Date of Approval	Question	Answer
			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 percent 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 less than 2-fold, it is greater than 20 percent 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 percent 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 less than 2-fold, and it is less than 20 percent 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 drug-drug interaction (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

Number	Date of Approval	Question	Answer
			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 cutoff values for drugs as precipitant of transporters that are not listed in Table 1?	For the transporters listed in Table 1, cutoff 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., organic cation transporter 1 (OCT1), multidrug resistance-associated protein 2 (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, cutoff values for transporters that are not listed in Table 1 may be deduced from the cutoff values from transporters listed in Table 1 when the similarity in organ and the cellular localization of the transporter are taken into consideration.

[*] Steinbronn C, Yang X, Yu J, et al., 2021, Do Inhibitory Metabolites Impact DDI Risk Assessment? Analysis of In Vitro Data From NDA Reviews Between 2013 and 2018, Clin Pharmacol Ther, 110(2):452–463.

III. CLINICAL EVALUATION (3)

Table 3. Q&A for Section III (3) of ICH M12

Number	Date of Approval	Question	Answer
3.1	May, 2024	What are the unique considerations regarding drug-drug interaction (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.

IV. REPORTING AND INTERPRETING CLINICAL DRUG-DRUG INTERACTION STUDY RESULTS (4)

Table 4. Q&A for section IV (4) of ICH M12

Number	Date of Approval	Question	Answer
4.1	May, 2024	How is the number of subjects determined for drug-drug interaction (DDI) studies?	As stated in the guidance, 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 to 20 subjects, but larger studies may be needed, for example, when variability is high or based on the specific objectives of the study.

V. APPENDIX (5)

Table 5. Q&A for Appendix B (Section 7.3) of ICH M12

Number	Date of Approval	Question	Answer
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.

Number	Date of Approval	Question	Answer
			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. Because 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, nonspecific 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 unbound inhibition constant causing half-maximal inactivation ($K_{i,u}$) or unbound half-maximal inhibitory concentration ($IC_{50,u}$), 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.

Number	Date of Approval	Question	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.