独立行政法人 医薬品医療機器総合機構
Pharmaceuticals and Medical Devices Agency

2023年12月20日
第48回ICH即時報告会

ICH M12: Drug Interaction Studies
薬物相互作用試験

M12 Regulatory Chair, Topic Leader
医薬品医療機器総合機構 審査マネジメント部

石黒 昭博

Regulatory documents on drug interaction evaluation in EU/Japan/US

2012

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 June 2012
CPMP/EWP/560/95/Rev. 1 Corr. 2**
Committee for Human Medicinal Products (CHMP)

Guideline on the investigation of drug interactions

Concept paper on a revision of guideline, 2017

Final Draft, 2014

2018

薬生薬審発 0723 第 4 号
平 成 30 年 7 月 23 日

各 都道府県 保健所設置市 特別区 衛生主管部（局）長 殿

厚生労働省医薬・生活衛生局医薬品審査管理課長
（ 公 印 省 略 ）

「医薬品開発と適正な情報提供のための薬物相互作用ガイドライン」について

Draft Guidance, 2012

Draft Guidance (*In vitro* / Clinical drug interaction), 2017

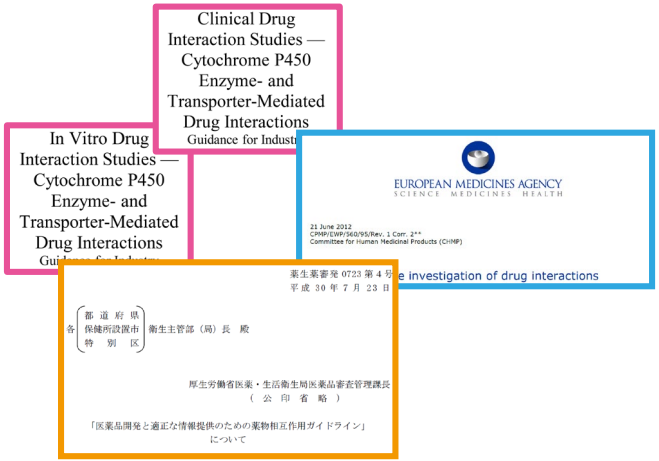
2020

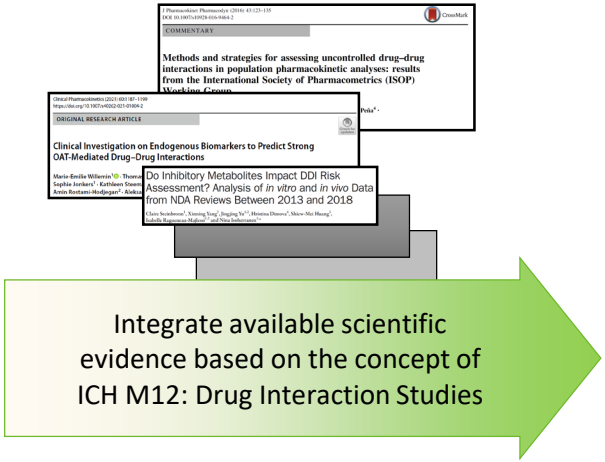
In Vitro Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions
Guidance for Industry

Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions
Guidance for Industry

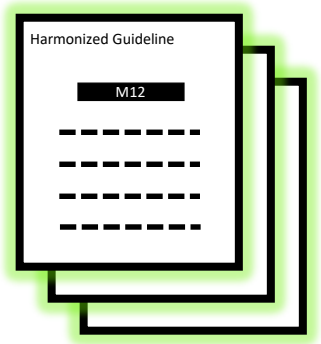
ICH M12 EWG (Drug Interaction Studies) is active from 2019

Goal of developing harmonized guideline on Drug Interaction Studies





ICH harmonisation for better health



- Guideline on Pharmacokinetic interactions mediated via metabolic enzymes and transporters
  - Help reduce uncertainty for the pharmaceutical industries and allow them to use a more global approach to assess DDI liability of their drugs
  - Lead to more efficient utilization for resources and help bring drugs to the global market more quickly for patients who need them

ICH M12 harmonization work

- **Rapporteur** Rajanikanth Madabushi (FDA, United States)
- **Regulatory Chair** Akihiro Ishiguro (MHLW/PMDA, Japan)

ANVISA, Brazil ; Luiza Novaes Borges

CIOMS; Hervé Le Louet

EC, Europe; Carolien Versantvoort, Elin Lindhagen

EFPIA; Sheila Peters, Venkatesh Pilla Reddy

FDA, United States; Kellie Reynolds, Xinning Yang

IFPMA; Tao Xiaolu

IGBA; Michael Forstner

JPMA; So Miyoshi, Ryota Shigemi

MFDS, Republic of Korea; Ji Sun Kim

MHLW/PMDA; Motohiro Hoshino, Akihiro Ishiguro

NMPA, China; Shujun FU, Li Li

PhRMA; Heidi Einolf, Vikram Sinha

Swissmedic, Switzerland; Matthias Roost

TFDA, Chinese Taipei; Meng-Syuan Yang

TGA, Australia; Irene Horne

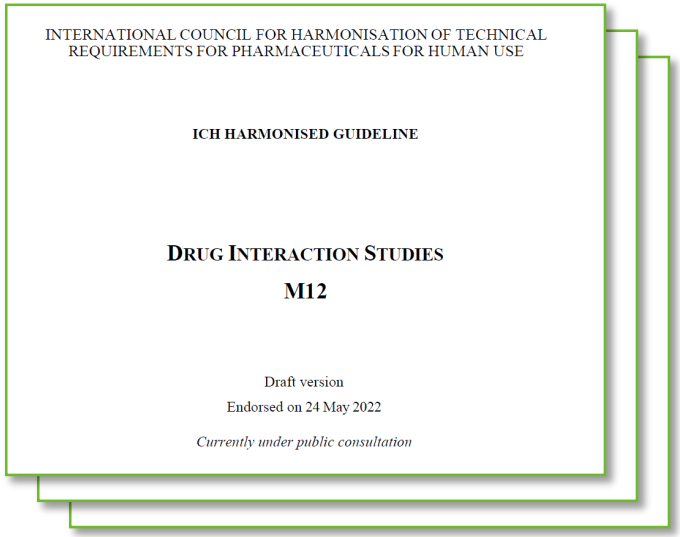
Draft (step 2b) is on MHLW website since Aug 2022
Public consultation ended Oct 2022

Draft guideline can be found on MHLW and ICH website

https://www.ich.org/page/multidisciplinary-guidelines

Table of Contents of M12

1. Introduction
2. *In vitro* evaluation
3. Clinical evaluation
4. Other topics
   - Pharmacogenetics
   - Therapeutic Protein DDIs
5. Reporting and interpreting clinical DDI study results
6. Risk assessment and management
7. Appendices
   - Glossary
   - Protein Binding
   - *In vitro* evaluation of metabolism/transporter-based DDIs
   - Predictive modeling
   - List of drugs that can be used in *in vitro*/clinical studies
8. References


INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

DRUG INTERACTION STUDIES

M12

Draft version

Endorsed on 24 May 2022

Currently under public consultation

https://public-comment.e-gov.go.jp/servlet/PcmFileDownload?seqNo=0000239543

Progress made at the Prague meeting

- Step 3: Addressing Public Consultation Comments
- Implemented a shared plan to address about 1000 comments we received through public consultation
- Developed and discussed specific proposals
  - Text updates
  - New content (Endogenous Biomarkers and Protein Binding)
  - Q&As for the topics identified at the Interim Meeting in Geneva
- Gained general alignment of the EWG on edits for several sections in the guideline and several Q&As
  - Drafting team initiated incorporating the aligned text

✓ **Working Group progressing as planned**

- ✓ **Addressed all comments identified by the subgroups**
- ✓ **Identified and prioritized 9 questions, developed answers and gained EWG alignment (e.g., Mass Balance, DDI study with contraceptive steroids, Sample size for clinical DDI studies, *In vitro* experimental methodology)**

Endogenous Biomarkers

976 ***3.2.5.2 Investigational Drug as an Inhibitor of Transporters***

993 Recent literature reports indicate potential utility of endogenous substrates for some drug
994 transporters (33-37). Evaluating the change in exposure of the endogenous substrate when the
995 investigational drug is administered may provide information regarding the drug's potential as a
996 transporter inhibitor.

Latest findings published after reaching Step2b suggest use of endogenous substrates as alternative approach of drug interaction evaluation

97 3.1 Types of Clinical DDI Studies (Terminology) 19
98 *3.1.1 Standalone and Nested DDI Studies* *19*
99 *3.1.2 DDI Studies with Index Perpetrators and Index Substrates* *19*
100 *3.1.3 DDI Studies with Expected Concomitant Drugs* *20*
101 *3.1.4 Cocktail Approach* *20*

✓ **"Biomarker Approach" as a type of Clinical DDI Studies**
✓ **Considerations for Biomarker Approach including an example of plasma coproporphyrin I (CP-I) for evaluation of hepatic OATP1B inhibition potential**

Protein Binding

298 Considering uncertainties in protein binding measurements for highly bound drugs, i.e., >99%
299 protein binding, $f_{u,p}$ (fraction unbound in plasma) should be set at 0.01 (i.e. 1%). It is understood
300 that there have been advances in methodologies to measure $f_{u,p}$ for highly protein bound drugs,
301 and this is an area of active research. Hence, in some situations, the measured $f_{u,p}$ can be used if
302 the accuracy and precision of measurement is demonstrated. Such a demonstration should include
303 full validation data of the protein binding assay including bioanalytical method with appropriate
304 positive controls (i.e., drugs with high binding to relevant plasma proteins). Demonstration of
305 reproducible findings with different assays (e.g., ultrafiltration, equilibrium dialysis,
306 ultracentrifugation) increases the reliability of the $f_{u,p}$ measurement and is preferred. This

Availability of “Orthogonal Approaches” to establish novel and emerging protein binding assay for highly protein bound drugs

✓ **New text on method validation requirements for highly bound drugs in Appendix Section**

Work plan

Expected Completion date	Milestones
Dec 2023	*Initiate Internal Consultation*
Jan 2024	*Share draft Guideline document with PWP experts*
March 2024	Step 4 Sign-off and Adoption of the final guideline

独立行政法人 医薬品医療機器総合機構
Pharmaceuticals and Medical Devices Agency

Thank you