Welcome to the webinar...

We will begin shortly

PROVEN GLOBAL CONTRACT RESEARCH EXPERTISE
FROM DISCOVERY THROUGH CLINICAL SUPPORT

Highlights of the In Vitro Sections of the Draft ICH Drug Interaction Studies Guideline and Comparison with Current Guidance

Brian Ogilvie, Ph.D.

XenoTech Vice President of Scientific Consulting

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Brian W. Ogilvie, Ph.D.
VP Scientific Consulting
Sekisui XenoTech, LLC
Kansas City, Kansas
Phone: 913.438.7450
Email: bogilvie@xenotechllc.com

BREAKING NEWS

XenoTech

Joins

BIOIVT

[Press Release]

BioIVT Acquires XenoTech, a Leading Provider of Products and Services for Preclinical Testing of New Drug Candidates

September 12, 2022

XenoTech specializes in providing ADME-Tox products and research services, in particular drug metabolism and pharmacokinetics (DMPK) and drug-drug interaction (DDI) studies

Westbury, NY – BioIVT, a leading provider of biospecimens, research models and services for drug and diagnostic development, today announced that it has acquired XenoTech, a provider of products for ADME-Tox *in vitro* models and contract research services, from Sekisui Chemical, based in Japan. XenoTech specializes in ADME, DMPK and DDI testing of potential drug candidates.

This transaction demonstrates BioIVT's continuing commitment to provide its biopharmaceutical customers with a comprehensive portfolio of research models and services to help them reach their R&D goals faster.

"XenoTech has a well-established and excellent reputation for producing microsomes, subcellular fractions, and for designing implementing ADME-Tox studies on a contract research basis," said BioIVT Chief Executive Officer (CEO) Dr. Richard Ha... The XenoTech and BioIVT product portfolios are complementary, and when combined, will enable smarter science and ...celerate medical breakthroughs that enhance and extend lives by delivering personalized biospecimen solutions to life ...ience and diagnostic industries. We are also delighted to have this opportunity to expand our highly respected scientific team with the addition of experienced researchers from XenoTech."

"My colleagues and I are looking forward to joining BioIVT and starting the next exciting phase of our ...rate growth," said Dr. Darren Warren, CEO of XenoTech. "We built our business by taking a consultative approach to everything we do, whether it is helping researchers identify products with the right characteristics or recommending specific study programs. BioIVT shares our commitment to science and producing high quality products, and our desire to partner with drug researchers in their quest to develop new therapies to meet unmet medical needs."

XenoTech's product lines, which include best-in-class microsomes, complement BioIVT's portfolio of hepatocytes and other hepatic products. XenoTech's expertise also combines well with BioIVT's strengths in drug transporter research, B-CLEAR® disposition studies, long-term HEPATOPAC® models, and other proprietary methodologies and will increase BioIVT's capabilities to support and accelerate customer research.

XenoTech will continue to operate out of its headquarters in Kansas City, KS. Financial details about this transaction were not disclosed.

"...opportunity to expand our scientific team..."

- Richard Haigh, CEO BioIVT

"...(we take) a consultative approach to everything we do..."

- Darren Warren, CEO XenoTech

Complementary product and research services portfolios

Presentation Outline

1. Overview of the draft ICH M12 Guideline
2. Summary of major points
3. Timing of *in vitro* studies
4. Evaluating test drugs as victims according to ICH, FDA, PMDA and EMA
5. Evaluating test drugs as perpetrators according to ICH, FDA, PMDA and EMA
6. DDI assays with metabolites
7. Experimental considerations from the appendices
8. New modalities
9. Conclusions

Regulatory guidance for DDIs (1)

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

Guidance for Industry

Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

FDA: Final 2020

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

January 2020
Clinical Pharmacology

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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

EMA: Final 2013

Guideline on the investigation of drug interactions

Discussion in the Efficacy Working Party (EWP)	June/October 1996 February 1997
Transmission to the CPMP	March 1997
Transmission to interested parties	March 1997
Deadline for comments	September 1997
Re-submission to the EWP	December 1997
Approval by the CPMP	December 1997
Date for coming into operation	June 1998
Draft Rev. 1 Agreed by the EWP	April 2010
Adoption Rev. 1 by CHMP for release for consultation	22 April 2010
End of consultation Rev. 1 (deadline for comments)	31 October 2010
Agreed by Pharmacokinetics Working Party	February 2012
Adopted by CHMP	21 June 2012
Date for coming into effect	1 January 2013

This guideline replaces guideline CPMP/EWP/560/95.

Keywords	*Interaction, guideline, metabolism, inhibition, induction, transport, enzyme, transport protein, transporter, absorption, food, distribution, PBPK, herbal, SmPC*

* The correction concerns section 5.3.4.1 (p 26) and the corresponding decision tree no. 6 (p 61) to read "if the observed KI value is lower or equal to /.../"; Appendix VII, Table 5 to read "See section 5.4.2".* Decision tree 4.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 Facsimile +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

An agency of the European Union

事　務　連　絡
平成 31 年 2 月 8 日

各都道府県衛生主管部（局）薬務主管課　御中

PMDA: Final 2018

厚生労働省医薬・生活衛生局医薬品審査管理課

「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」等の英文版の送付について

標記について、別添１及び２のとおり取りまとめましたので、貴管下関係業者に対して周知方お願いします。

別添１　Guideline on drug interaction for drug development and appropriate provision of information

別添２　Question and Answer for the "Guideline on drug interaction for drug development and appropriate provision of information"

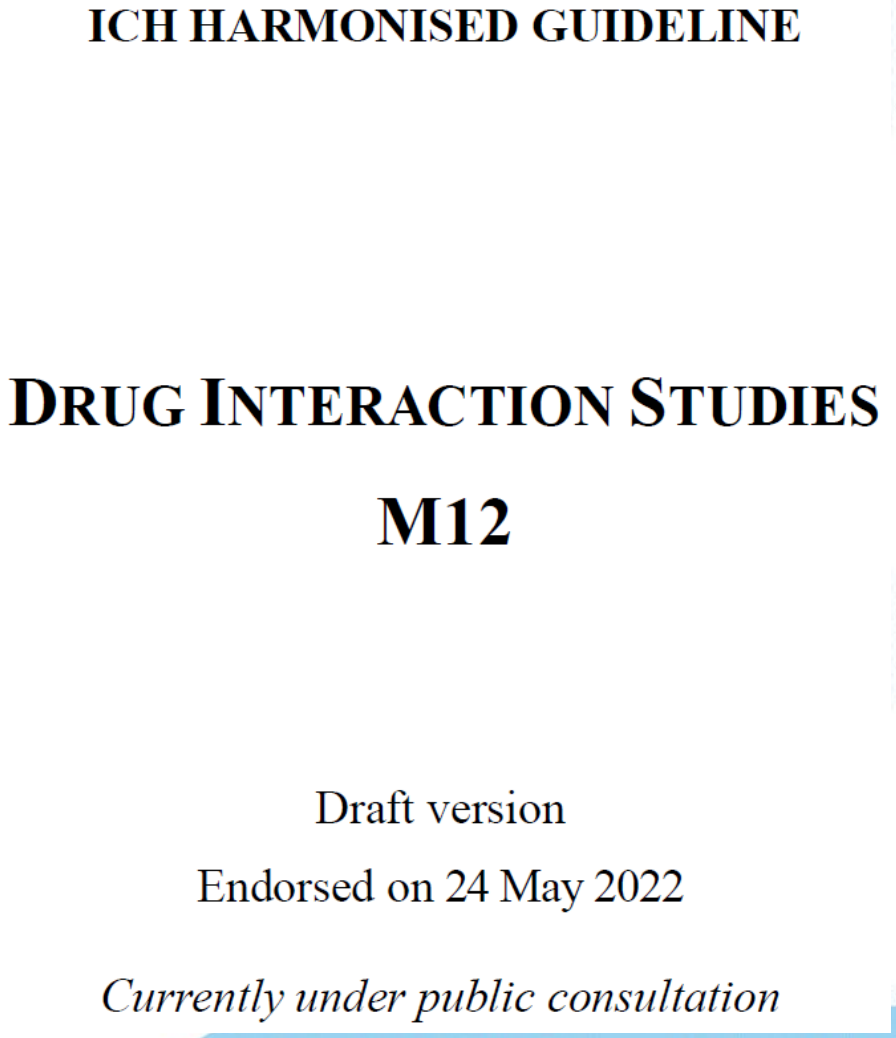
ICH – International Council for Harmonisation

- Established 1990
- Members of regulatory authorities and the pharmaceutical industry organized to discuss scientific and technical aspects of pharmaceuticals to develop harmonized guidelines
- The ICH mission is to achieve greater harmonization worldwide to ensure that safe, effective and high quality medicines are developed . . . in the most efficient manner [while] meeting high standards
- Examples include safety guidance in cancer, QT prolongation, BCS biowaiver

ICH harmonisation for better health

Regulatory guidance for DDIs (2)

ICH: One guidance to guide them all


ICH HARMONISED GUIDELINE

DRUG INTERACTION STUDIES

M12

Draft version

Endorsed on 24 May 2022

Currently under public consultation

- ICH guidelines: Usually replace most regional guidance documents
- FDA 8/24/22: "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"
- Will not be finalized until ~ April 2024

FDA Draft Guidance for Industry M12 Drug Interaction Studies 8/24/22

Outline of in vitro ICH M12 sections

2.1 Evaluation of Metabolism-Mediated Interactions

2.1.1 Drug as a Substrate of Metabolizing Enzymes
2.1.2 Drug as an Inhibitor of CYP Enzymes
2.1.3 Drug as an Inhibitor of UGTs
2.1.4 Drug as an Inducer of CYP Enzymes

2.2 Evaluation of Transporter-Mediated Interactions

2.2.1 Drug as a Substrate of Transporters
2.2.2 Drug as an Inhibitor of Transporters
2.2.3 Drug as an Inducer of Transporters

2.3 DDI Potential of Metabolites

2.3.1 Metabolite as a Substrate
2.3.2 Metabolite as an inhibitor
2.3.3 Metabolite as an Inducer

4.2 Therapeutic Protein DDIs

4.2.1 Proinflammatory Cytokine-Related Mechanism
4.2.2 Antibody-Drug Conjugates

7. Appendices
7.1 In Vitro Evaluation of Metabolism-Based DDIs
7.2 In Vitro Evaluation Of Transporter-Based DDIs
7.3. Predictive Modeling
7.4. List of Drugs that can be used in In Vitro Studies

Appendices: Provide relatively detailed guidance for in vitro assay design, test system considerations, etc.

Summary of major points in the draft 2022 ICH M12

- Title: Simply “Drug-Drug Interaction Studies”
- Covers both in vitro and clinical DDI studies in one guideline
- Incorporates many aspects already in FDA, EMA and PMDA guidance documents
  - As a CRO, we typically already cover most aspects since sponsors usually plan to apply for marketing authorization in Europe and USA, sometimes Japan
- Includes mention of transporter induction if CYPs are induced – but refers to clinical section
- Much more detailed assay methods are provided than in current guidance documents
- Includes therapeutic proteins, antibody drug conjugates and pharmacogenetics
- Other major points covered in later slides

Timing of in vitro DDI studies

FDA 2020

- Work backwards from final FDA clinical guidance
  - When are DDI results needed?
  - Before administration to patients: "Inadequate studies of DDIs can hinder the FDA's ability to determine the benefits and risks of [a] . . . drug and . . . result in restrictive labeling, [PMRs or PMCs], and/or **delayed approval**"
  - "collect enough DDI information to prevent patients from being unnecessarily excluded from any clinical study because of their concomitant medication use"

ICH M12 2022

- Drug as a substrate of metabolic enzymes generally should be obtained before starting phase 1 (no mention of "patients")
- The results of the mass balance study should generally be available before starting phase 3
- If a drug has limited absorption or is expected to undergo significant active hepatic uptake, biliary excretion or active renal secretion as unchanged drug, the relevant transporters should be identified in vitro before initiating clinical studies in patients to avoid protocol restrictions.
- Perpetrator potential data on the major cytochrome P450 (CYP) enzymes and transporters should generally be available before administering the drug to patients.
- DDI potential of metabolites with significant plasma exposure or pharmacological activity should be considered similarly as for the parent drug, but these investigations can generally be completed later in development when more knowledge about the exposure and activity of metabolites is available

Evaluating test drugs as victims according to ICH, FDA, PMDA, and EMA

Agency	Date	Scope – CYP enzymes	Other DMEs
ICH	**2022**	CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and CYP3A4/5 * 2nd tier: CYP2A6, 2E1, 2J2, 4F2	**Phase I:** CES, MAO, FMO, XO, AO, ADH/ALDH **Phase II:** UGT1A1, 1A3, 1A4, 1A6, 1A9, 1A10, 2B4, 2B7, 2B10, 2B15, and 2B17 SULTs, GSTs, NATs
FDA	2020	CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and CYP3A4/5 2nd tier: CYP2A6, 2E1, 2J2, and 4F2	**Phase I:** CES, MAOs, FMOs, XO, AO, ALDHs, ADHs Phase II: UGTs, SULTs
PMDA	2018	CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4, and 3A5 2nd tier: CYP2A6, 2E1, 2J2, and 4F2	**Phase I:** MAOs, FMOs, XO, AO, ALDHs, ADHs, DPD Phase II: UGTs (“e.g., UGT1A1 and 2B7”)
EMA	2013	Specifies test systems, not enzymes: “CYP and UGT enzymes are present in all systems mentioned”	Notes SULTs, GSTs, ALDHs and ADHs in S9 and hepatocytes

*ICH notes that “if the drug is not found to undergo significant metabolism by these major CYPs, [others] can be investigated”

Evaluating test drugs as transporter substrates (victims) according to ICH, FDA, PMDA and EMA

Agency	Scope – Transporters	Comment
ICH, FDA & PMDA (2022, 2020 & 2018)	Intestinal efflux: P-gp and BCRP	Orally administered investigational drugs – nearly always
	Hepatic uptake: OATP1B1 and OATP1B3	Yes, if hepatic metabolism or biliary secretion ≥25% of total clearance or hepatic uptake is important. Consider the "drug's physiological properties . . ." ICH: Also if target is in the liver
	Renal uptake/bidirectional: OAT1, OAT3, OCT2, MATEs	Yes, if active renal secretion ≥25% of total clearance ICH: Also if renal toxicity observed
ICH 2022	**Consider** MRP2, OCT1 and OATP2B1	"Additional transporters can be decided on a case-by-case basis"
EMA 2013	OATPs if ≥ 25% "hepatic elimination". Other "in vitro … studies [that] isolate the effect of a specific transporter" if ≥ 25% elimination due to renal, biliary or gut wall secretion. Also evaluate major active (≥50%) or toxic metabolites.	

Transporters – Simplified interpretation of substrate (victim) potential

Agency	Transporters	Simplified interpretation of positives
ICH, FDA & PMDA (**2022**, 2020 & 2018)	Intestinal efflux P-gp and BCRP	Net flux or efflux ratio ≥2, significantly inhibited by one or more known inhibitors (ICH: >50%)
	Hepatic uptake OATP1B1 and OATP1B3	Significant uptake (e.g., ≥2-fold in controls) and inhibition by one or more known inhibitors (ICH: >50%)
	Renal uptake/bidirectional OAT1, OAT3, OCT2, MATEs	Significant uptake (e.g., ≥2-fold in controls) and inhibition by one or more known inhibitors (ICH: >50%)

ICH has additional considerations in the appendices, and mentions MRP2, OCT1 and OATP2B1

Drug metabolizing enzyme inhibition (perpetrator) - Scope

Agency	Date	Scope – CYP enzymes (direct & TDI)	Other drug-metabolizing enzymes (DMEs)
ICH	**2022**	CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and CYP3A (with 2 substrates)	**If direct glucuronidation**: "UGTs, including UGT1A1 and UGT2B7"
FDA	2020	CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and CYP3A (with 2 substrates)	None
PMDA	2018	CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and CYP3A (with 2 substrates)	UGT1A1 & UGT2B7 and others
EMA	2013	CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and CYP3A (with 2 substrates)	UGT1A1 & UGT2B7 and "study inhibition of UGTs known to be involved in drug interactions"

Note: ICH also says "When an investigational drug is to be used with another drug that is mainly metabolized by direct glucuronidation, it is recommended to evaluate the in vitro potential inhibitory effect of the investigational drug on the [UGTs] responsible for the elimination of the other drug."

Interpretation of reversible hepatic CYP inhibition

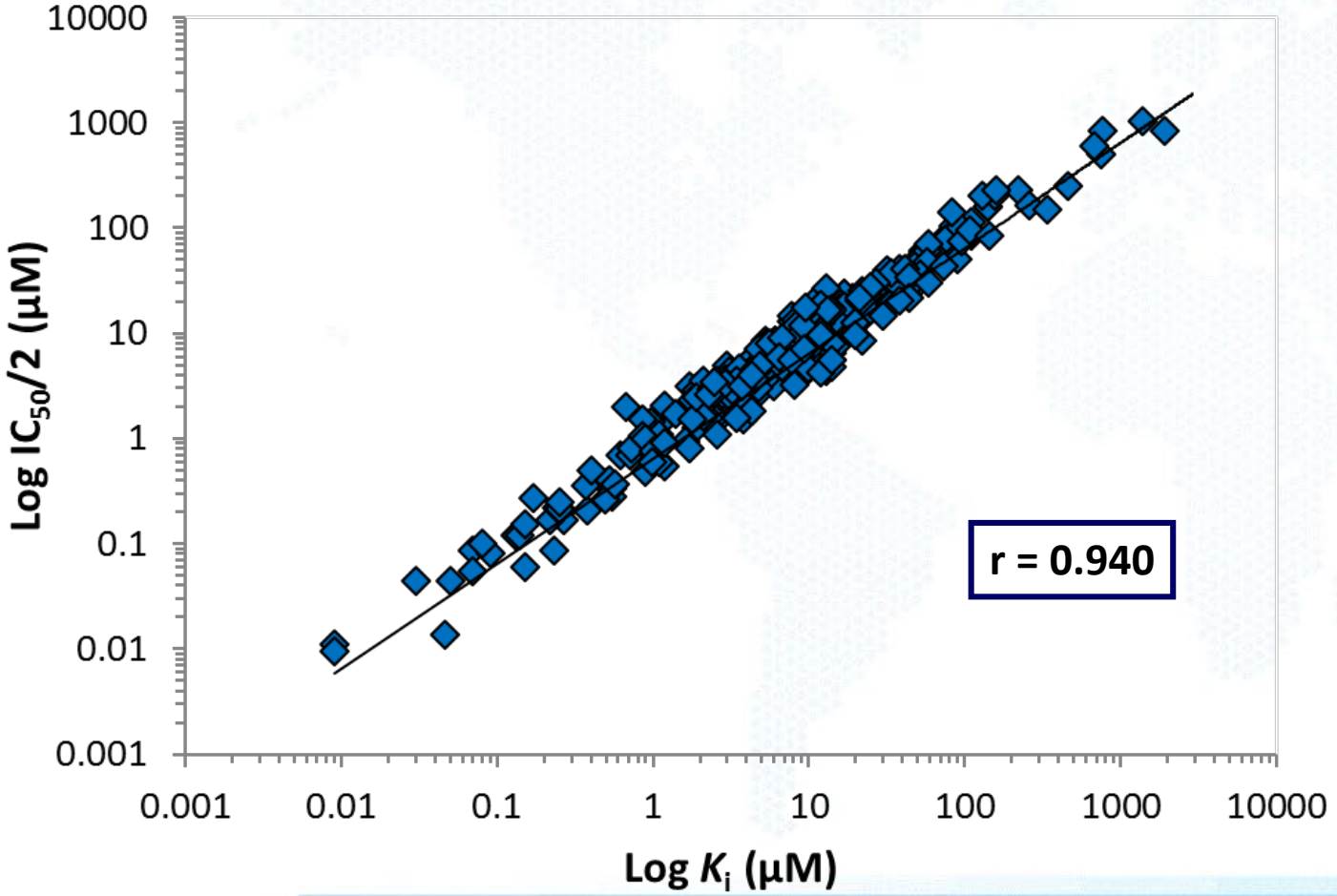
Agency	Date	Equation (as written)	Unbound or total concentration?	Cutoff for a positive result	Comment
ICH	**2022**	$\frac{C_{max,u}}{K_{i,u}}$	Unbound C_{max} Unbound K_i	> 0.02	Equivalent To EMA
FDA	2020	$R_1 = 1 + \frac{I_{max,u}}{K_{i,u}}$	Unbound C_{max} Unbound K_i	≥ 1.02	Same
PMDA	2018	$R = 1 + \frac{[I]}{K_i}$	Unbound C_{max} Not specified for K_i	≥ 1.02	Same
EMA	2013	$\frac{[I]}{K_i}$	Unbound C_{max} Not specified for K_i	≥ 0.02	Equivalent (it's missing the 1+ factor)

ICH and FDA cite Haupt … Parkinson (2015) *DMD* 43:1744 to allow Ki values to be calculated as $IC_{50}/2$ when [S] = Km.

Note: PMDA and EMA recommend estimating unbound [I] in vitro due to non-specific binding, but not included in equations.

For CYP inhibition, does $IC_{50}/2$ really equal K_i when [S] = Km?

Correlation of Estimated K_i and Experimental K_i Values for direct inhibition



Yes: Data from 343 experimentally determined Ki values correlate with predicted Ki values from $IC_{50}/2$ when [S] = Km.

This is cited in the draft ICH and final 2020 FDA guidance

Based on the **Cheng-Prusoff equation** for competitive inhibition: Cheng & Prusoff (1973). *Biochem Pharmacol* 22:3099

$$K_i = \frac{IC_{50}}{1 + \frac{[S]}{K_m}}$$

Haupt ... Parkinson (2015) *DMD* 43:1744

Interpretation of reversible inhibition of intestinal CYP3A enzymes

Agency	Date	Equation (as written)	Concentration Nominal or unbound?	Cutoff for a positive result	Comment
ICH	**2022**	$\frac{[\frac{Dose}{250\ mL}]}{K_i}$	Notes 0.1 x maximum clinical dose in 250 mL Not specified for K_i	>10	Equivalent To EMA
FDA	2020	$R_{1,gut} = 1 + \frac{I_{gut}}{K_{i,u}}$	0.1 x Dose/250 mL Unbound K_i	≥ 11	Same
PMDA	2018	$R = 1 + \frac{I_g}{K_i}$	0.1 x Dose/250 mL Not specified for K_i	≥ 11	Same
EMA	2013	$\frac{[I]}{K_i}$	0.1 x Dose/250 mL Not specified for K_i	≥ 10	Equivalent (it's missing the 1+ factor)

Note: PMDA and EMA recommend estimating unbound [I] in vitro due to non-specific binding, but not included in equations.

Interpretation of irreversible inhibition of hepatic CYP enzymes

Agency	Equation (as written)	Unbound or total concentration?	Cutoff $\frac{k_{obs} + k_{deg}}{k_{deg}}$	Comment
ICH (2022)	$K_{obs} = \frac{k_{inact} \cdot 5 \cdot C_{max,u}}{K_{I,u} + 5 \cdot C_{max,u}}$	Unbound C_{max} Unbound K_I	>1.25	New equation
FDA (2020)	$K_{obs} = \frac{k_{inact} \cdot 50 \cdot I_{max,u}}{K_{I,u} + 50 \cdot I_{max,u}}$	Unbound C_{max} Unbound K_I	≥ 1.25	Same
PMDA (2018)	$K_{obs} = \frac{k_{inact} \cdot 50 \cdot [I]}{K_I + 50 \cdot [I]}$	Unbound C_{max} Not specified for K_I	≥ 1.25	Same
EMA (2013)	$K_{obs} = \frac{k_{inact} \cdot [I]}{K_I + [I]}$	Unbound C_{max} Not specified for K_I	≥ 1.25	Same cutoff, different equation

Note: ICH has additional experimental considerations detailed in the appendices

PMDA and EMA recommend estimating unbound [I] in vitro due to non-specific binding, but not included in equations.

Interpretation of irreversible inhibition of intestinal CYP3A

Agency	Equation	Unbound or total concentration?	Cutoff $\frac{k_{obs} + k_{deg}}{k_{deg}}$	Comment
ICH (2022)	There isn't one	?	?	?
FDA (2020)	There isn't one (i.e., no "$R_{2,gut}$")	?	?	?
PMDA (2018)	$K_{obs} = \frac{k_{inact} \cdot 0.1 \cdot [I]_g}{K_I + 0.1 \cdot [I]_g}$	$[I]_g$ = dose/250 mL Not specified for K_I	≥ 1.25	Use for FDA and ICH?
EMA (2013)	$K_{obs} = \frac{k_{inact} \cdot [I]}{K_I + [I]}$	$[I]$ = dose/250 mL Not specified for K_I	≥ 1.25	Same cutoff, different equation

Interpretation of CYP Induction data (Basic R_3 method)

Agency	Equation (as written)	Measure *in vitro* concentration of test drug?	Cutoff for a positive result	Comment
ICH 2022	$R = \frac{1}{1 + d \cdot \left(\frac{E_{max} \cdot 10 \cdot C_{max,u}}{EC_{50} + 10 \cdot C_{max,u}}\right)}$	Yes	< 0.8	Similar to FDA and PMDA
FDA 2020	$R_3 = \frac{1}{1 + d \cdot \left(\frac{E_{max} \cdot 10 \cdot I_{max,u}}{EC_{50} + 10 \cdot I_{max,u}}\right)}$	Yes	≤ 0.8	Same
PMDA 2018	$R = \frac{1}{1 + d \cdot \left(\frac{E_{max} \cdot 10 \cdot [I]}{EC_{50} + 10 \cdot [I]}\right)}$	Yes	≤ 0.8	Same
EMA 2013	Has an "R_3" type equation for use in a mechanistic static model but not as a standalone static model with its own cutoff value	Yes	Not specified	

Transporter inhibition - Scope

Agency	Date	Scope – Transporters	Comment
ICH	**2022**	Same as FDA and PMDA **+** BSEP, MRP2, OCT1, and OATP2B1 on a case by case basis	TDI of OATPs But follow current literature
FDA	2020	Intestinal (renal/hepatic) efflux: P-gp and BCRP Hepatic uptake: OATP1B1 and OATP1B3 Renal uptake: OAT1, OAT3, and OCT2 Bidirectional renal/hepatic: MATE1 and MATE2-K	TDI of OATPs
PMDA	2018	Same (n = 9)	Same
EMA	2013	Same + OCT1 (hepatic uptake) and BSEP (hepatotoxicity marker) (n = 11)	

ICH: If data are used for PBPK, determine Ki. Drug concentration cannot exceed solubility or cytotoxicity. If high enough concentrations not reached, “in vivo assessment” is recommended.

Intestinal P-gp and BCRP inhibition – Equations and cutoffs

Agency	Equation (as written)	*In vivo* concentration Nominal or unbound *in vitro* concentration?	Cutoff for a positive result	Comment
ICH 2022	$\frac{Dose/250mL}{K_i \text{ or } IC_{50}}$	Dose/250 mL Not specified	>10	Equivalent to FDA and PMDA
FDA 2020	$\frac{I_{gut}}{IC_{50}\ (OR\ K_i)}$	Dose/250 mL Not specified	≥ 10	Same ↕ Same
PMDA 2018	$\frac{I}{IC_{50}}$	Dose/250 mL Not specified	≥ 10	
EMA 2013	$\frac{0.1 \cdot Dose/250mL}{K_i}$	0.1 x Dose/250 mL Not specified	>1	Equivalent: Cutoff is 10 if Dose/250 mL is used

ICH 2022: "Other cut-off values can be proposed if justified based on in vitro to in vivo extrapolation and a calibration of the specific in vitro systems with known inhibitors and non-inhibitors of these transporter systems."

OATP1B1 and OATP1B3 inhibition – Equations and cutoffs

Agency	Equation (as written)	*In vivo* concentration Unbound *in vitro* concentration?	Cutoff for a positive result	Comment
ICH 2022	$\frac{C_{max,inlet,u}}{K_i \text{ or } IC_{50}}$	Unbound inlet Not specified	> 0.1	R_b not mentioned in this section
FDA 2020	$R = 1 + \frac{f_{u,p} \cdot I_{in,max}}{IC_{50}}$	Unbound inlet Not specified	≥ 1.1	R_b used in $I_{in,max}$ equation
PMDA 2018	$1 + \frac{f_{u,b} \cdot I_{inlet,max}}{K_i}$	Unbound inlet Not specified	≥ 1.1	R_b implied ($f_{u,b}$ is used)
EMA 2013	$\frac{25 \cdot Imax_{u,inlet}}{K_i}$	Unbound inlet Not specified	> 1	Equivalent cutoff is 1.04

For discussion of R_b term, see Parkinson A. *Drug Metab Dispos* 47:779-784, 2019

OAT1, OAT3, OCT2 and MATEs inhibition – Equations and cutoffs

Agency	Equation (as written)	*In vivo* concentration Unbound *in vitro* concentration?	Cutoff for a positive result	Comment
ICH 2022	$\frac{C_{max,u}}{K_i \text{ or } IC_{50}}$	Unbound plasma C_{max} Not specified	> 0.1 MATEs > 0.02	MATEs back to more conservative EMA and PMDA criteria
FDA 2020	$\frac{I_{max,u}}{IC_{50}}$	Unbound plasma C_{max} Not specified	≥ 0.1	Cutoff for MATEs increased to ≥ 0.1
PMDA 2018	$1 + \frac{unbound\ C_{max}}{K_i}$	Unbound plasma C_{max} Not specified	≥ 1.1	Equivalent to FDA cutoff (Cutoff for MATEs is ≥ 1.02)
EMA 2013	$\frac{50 \cdot Cmax_u}{K_i}$	Unbound plasma $C_{max,ss}$ Not specified	>1	Equivalent to PMDA cutoff of 1.02

ICH does not explicitly cover BSEP, MRP2, OCT1, and OATP2B1 in cutoff equations

DDI assays with metabolites

- Generally not needed if there will be clinical DDI studies of the parent
- Metabolites as substrates:
  - If a metabolite might have a safety impact
  - If on-target effect of a metabolite is greater than the parent
  - Differs from FDA 2020 guidance for metabolites with >50% of overall activity
  - Additional details in guideline
- Metabolites as inhibitors:
  - Yes if $AUC_{metabolite}$ > 25% AUC_{parent} and >10% $AUC_{total\ drug\ related\ material}$
  - More consistent with 2013 EMA approach
  - FDA consideration of polarity of metabolite relative to parent removed
- Similar approaches used for transporters and CYPs
- Generally no assessment of metabolites as inducers (unless a prodrug or a major metabolite formed extra-hepatically)

ICH Considerations from the appendices (1)

General aspects

- Experimental details for in vitro studies
- Lists of drugs that can be used in in vitro studies of CYPs, UGTs and transporters
- Predictive modelling approaches (i.e., basic as well as static mechanistic and PBPK models)
- Applications of modelling:
  - Support some clinical recommendations when a clinical DDI study has not been performed
  - Decide if a clinical DDI study is needed

ICH Considerations from the appendices (2)

Test systems

- Human liver microsomes (HLM), “a pool of at least 10 donors is suggested”
- “S9; containing microsomal as well as cytosolic enzymes such as sulfotransferases, glutathione transferases, aldehyde dehydrogenase, aldehyde oxidase and alcohol dehydrogenase”
- “Cytosol (adding co-factors as appropriate)”
- Recombinant human CYP and UGT enzymes (SULTs not mentioned)
- Hepatocytes: “For phenotyping and inhibition experiments, hepatocytes pooled from at least 10 donors is suggested, whereas for induction experiments at least 3 individual donors should be used” – unless a single culture is fully validated per the ICH M12
  - Note that for induction, mRNA is the endpoint except for CYP2C19 (use activity)
  - Test article concentration for induction is only 15 x $C_{max,u}$ not 30 x as in FDA

ICH Considerations from the appendices (3)

Time-dependent inhibition

- Can use the fold-shift in IC_{50} method (± NADPH):
  - However, "The degree of the fold-shift to establish a positive result would be dependent upon the demonstrated sensitivity of the experimental system used to detect known TDI compounds, particularly at least one with a lower fold-shift (e.g. ritonavir)"
- New method would *appear* to require two experiments:
  1. IC_{50} (or single concentration at 50 x $C_{max,u}$) for reversible inhibition (no dilution)
  2. IC_{50} with test article pre-incubated for 30 min ± NADPH followed by a 10-fold dilution prior to the substrate incubation ("standard dilution methods")
  - Goal is to decrease effect of direct inhibition
- Dilution should be used for K_I and k_{inact} experiments (after there is an indication of TDI in IC_{50} shift experiments)
- We detailed the challenges of using a dilution in IC_{50} shift experiments in 2011

See Parkinson A … Ogilvie BW. *Drug Metab Dispos* 39:1370-1387, 2011

Therapeutic Protein DDIs

- "In general, the risk of pharmacokinetic DDIs is lower for proteins. The in vitro assays that are applicable for small molecules are generally not applicable to proteins."
- "When evaluating the potential for a DDI between monoclonal antibodies and small molecules or between monoclonal antibodies, the mechanisms of a potential DDI should be considered, taking into account the pharmacology and clearance of the monoclonal antibodies as well as any co-administered medications in the patient population."

Proinflammatory Cytokine-Related Mechanism

- "Certain therapeutic proteins may exert an indirect effect on expression of CYP enzymes and thus affect the pharmacokinetics of small molecules."
- "The increase in cytokine levels as a result of drug treatment can be transient or persistent; sponsors should consider this increase when determining whether to conduct a DDI study as well as the design of that study."
- "If the investigational drug is a cytokine or a cytokine modifier, sponsors should consider whether to perform a clinical DDI study to evaluate the effects of the investigational therapeutic protein on sensitive substrates for CYP enzymes."

Antibody-Drug Conjugates

- "The small molecule drug component conjugated to the antibody component can be released in unconjugated form. Therefore, the DDI potential of both the antibody and the small molecule drug component should be considered"
- "In general, for the small molecule component, the potential to inhibit or induce enzymes and transporters should be addressed in line with what is described elsewhere."
- "It might be necessary to evaluate the small molecule component (administered as an ADC) as a *victim* drug, in particular if increased levels of free drug may be associated with safety concerns. Understanding the exposure-response relationship of the various moieties is important in determining whether to conduct DDI studies and their significance."

Conclusions: Harmonization is the goal

- Many details in the ICH are identical to the FDA 2020 final in vitro DDI guidance
- Incorporates some details from EMA and PMDA guidance
- Much more detailed than any of the other guidance documents with respect to assay designs included in the appendices
- Additional modalities included: therapeutic protein and suppression from cytokines and immunomodulators, antibody drug conjugates
- Consider adopting some of the ICH strategies now if your IND won't be submitted until 2024

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Thank You!