Comparison Between the US FDA, Japan PMDA and EMA In Vitro DDI Guidance: Are we Close to Harmonization?

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Outline

- Current guidance documents (US, Japan, Europe)
- Timing of *in vitro* studies
- Evaluating test drugs as victims
  - Enzymes of interest
  - Transporters of interest
- Evaluating test drugs as perpetrators
  - Basic models for interpretation

Due to time limits, several details cannot be covered today

2017 FDA and PMDA Draft DDI Guidance Documents

In Vitro Metabolism- and Transporter-Mediated Drug-Drug Interaction Studies

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Office of Clinical Pharmacology, Guidance and Policy Team at CDER_OCP_GPT@fda.hhs.gov.

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目次

Posted: 4 Sep, 2017

Comment period ended: 31 Oct, 2017

93 pages - (with EMA 2013: 153 pages; ~64,000 words)

New EMA Guideline?

- EMA: *Guideline on the investigation of drug interactions*

Revision 2	Concept paper	Published: 07/04/2017 Deadline for comments: 30/06/2017
Revision 1 *Current version*	Adopted guideline	In operation: 01/01/2013–present
	Currently under revision	
	Overview of comments	Published: 02/08/2013
	Draft guideline	Published: 30/04/2010
	Concept paper	Published: 24/07/2008

- Proposed timetable:
  - After receipt of comments "the draft Guideline will be consolidated and released for six months external consultation"
- EMA is working on the document – unlikely to be issued in 2018

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EMA Guideline link ; Q&As link; EMA Concept Paper link

Timing of in vitro studies in the FDA guidance

- Timing - Work backwards from FDA clinical guidance
  - When are clinical 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"

Timing of studies in the PMDA guidance

- Less direct than the FDA guidance, but early
  - "Usually, *in vitro* metabolism studies are carried out before the initiation of phase I studies" (e.g., major metabolite ID, pathways, plasma protein binding)
  - In vitro DDIs: "usually before the initiation of Phase III studies"

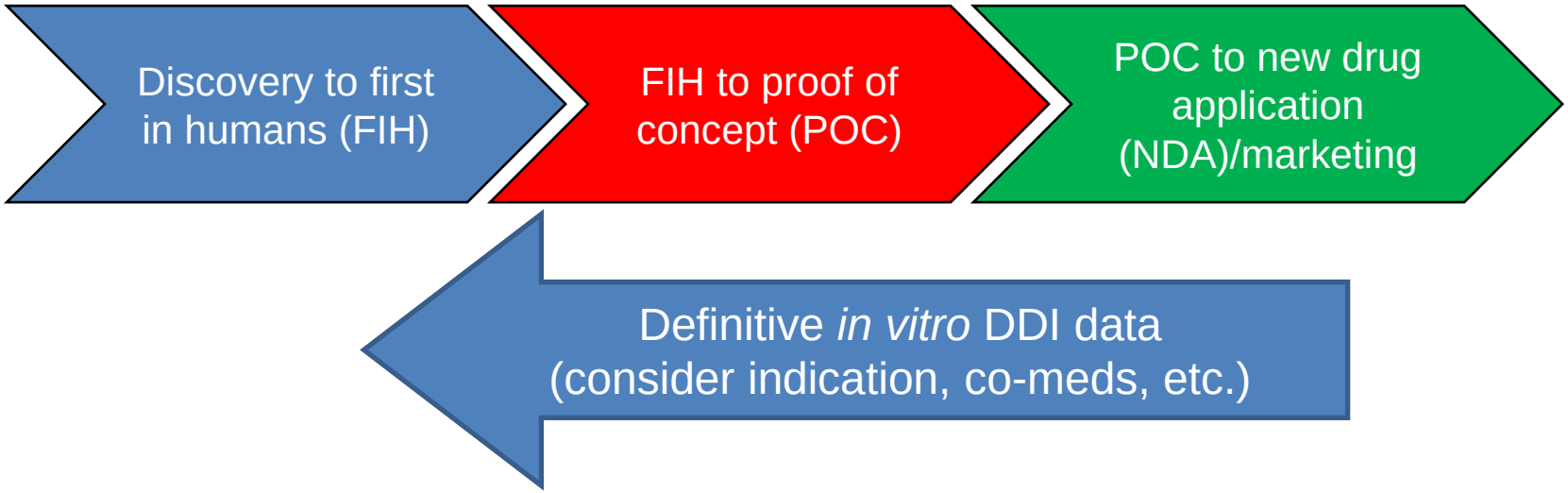

Figure adapted from Tweedie et al., *CPT*, **94**:1, 2013.

Strategy for timing of studies for US, Japan and EU

Unless you are seeking approval in only one market:

1. Victim potential (metabolism)
   - *In vitro* metabolite ID and reaction phenotyping: *Before* phase I
   - Covered in EMA 2013, now FDA and PMDA
2. Victim potential (transporters)
   - P-gp and BCRP substrate potential *before* phase I
   - Substrate potential for other transporters as early as possible (based on routes of elimination)

Strategy for timing of studies for US, Japan and EU (cont.)

3. Perpetrator potential
    - CYP inhibition and induction: *Before* phase I
    - *Strongly* implied in FDA 2017
    - Preferably before phase II in EMA 2013
4. Perpetrator potential (transporters)
    - Inhibition *before* phase I

- Complicated by lack of clinical exposure values
    - Base concentrations on solubility / cytotoxicity

Guidance for in vitro studies – Victim potential

Metabolism - Scope for victim potential

Agency	Date	Scope – CYP enzymes	Other DMEs
FDA	2017	CYP1A2, 2B6, 2C9, 2C8, 2C9, 2C19, 2D6, and CYP3A4/5 2nd tier: CYP2A6, 2E1, 2J2, and 4F2	**Phase I:** MAOs, FMOs, XO, ALDHs, ADHs **Phase II:** UGTs
PMDA	2017	CYP1A2, 2B6, 2C9, 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

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Additions relative to FDA 2017 in red

PMDA and FDA guidance for in vitro studies - Victims

Metabolism - Scope for victim potential (cont.)

- Also evaluate major active (≥50%) or toxic metabolites
- If ≥25% contribution of any one enzyme to elimination then conduct a clinical DDI study with strong inhibitor or inducer (both FDA and PMDA)

PMDA and FDA guidance for in vitro studies - Victims

Transporters – Scope for substrate potential

Agency	Scope – Transporters	Comment
FDA & PMDA	Intestinal efflux P-gp and BCRP*	**All** orally administered investigational drugs
	Hepatic uptake OATP1B1 and OATP1B3	Yes, if hepatic metabolism or bile secretion ≥25% of total clearance or unclear
	Renal uptake/bidirectional OAT1, OAT3, OCT2, MATEs	Yes, if active renal secretion ≥25% of total clearance or unclear

*FDA notes "*most* investigational drugs": not BCS1

PMDA: Other transporters to consider include OCT1 and MRP2

Transporters – Scope for substrate potential (cont.)

- Additional EMA (2013) considerations:
  - 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
  - Clinical evaluation?
    - . . . "when a candidate transporter has been identified . . . an *in vivo* study with a strong inhibitor is recommended"

PMDA and FDA guidance for in vitro studies - Victims

Transporters – Interpretation of substrate potential

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

Transporters – Clinical evaluation of substrates (1)

- FDA: If positive, *consider* clinical studies based on safety margin, *likely* co-medications that are *known inhibitors* of the transporters, etc.
  - Refers to clinical guidance for specific clinical designs
  - Also refers to the FDA DDI website for clinical inhibitors

Transporters – Clinical evaluation of substrates (2)

- PMDA: More nuanced
  - P-gp: consider GI absorption, brain distribution and risk of CNS toxicity and renal secretion
    - If substrate F_aF_g is ≥80% - no interaction presumed in gut
  - BCRP: High rate of polymorphisms in Japan
    - "currently difficult to design [DDI] studies using *in vivo* … inhibitors", but need to include in label

F_a = fraction absorbed; F_g = fraction escaping gut metabolism

Transporters – Clinical evaluation of substrates (3)

- PMDA (continued)
  - OATP1B1/1B3: Clinical DDI study with rifampin or cyclosporine recommended
  - OAT1/3: Clinical DDI study with probenecid recommended
  - MATEs: Clinical DDI study with cimetidine recommended
  - OCT2: "currently difficult to design [DDI] studies using *in vivo* … inhibitors", but need to include in label

Guidance for in vitro studies – Perpetrator potential

Reversible inhibition - Scope

Agency	Date	Scope – CYP enzymes	Other drug-metabolizing enzymes (DMEs)
FDA	2017	CYP1A2, 2B6, 2C9, 2C8, 2C9, 2C19, 2D6, and CYP3A (with 2 substrates)	None
PMDA	2017	CYP1A2, 2B6, 2C9, 2C8, 2C9, 2C19, 2D6, and CYP3A (with 2 substrates)	UGT1A1 & UGT2B7 **and others**
EMA	2013	CYP1A2, 2B6, 2C9, 2C8, 2C9, 2C19, 2D6, and CYP3A (with 2 substrates)	UGT1A1 & UGT2B7 (others as needed)

If the test drug is directly glucuronidated then test for inhibition of UGT1A1 & UGT2B7 and **other** UGT enzymes, namely those that directly glucuronidate the test drug

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Reversible inhibition of hepatic CYP enzymes

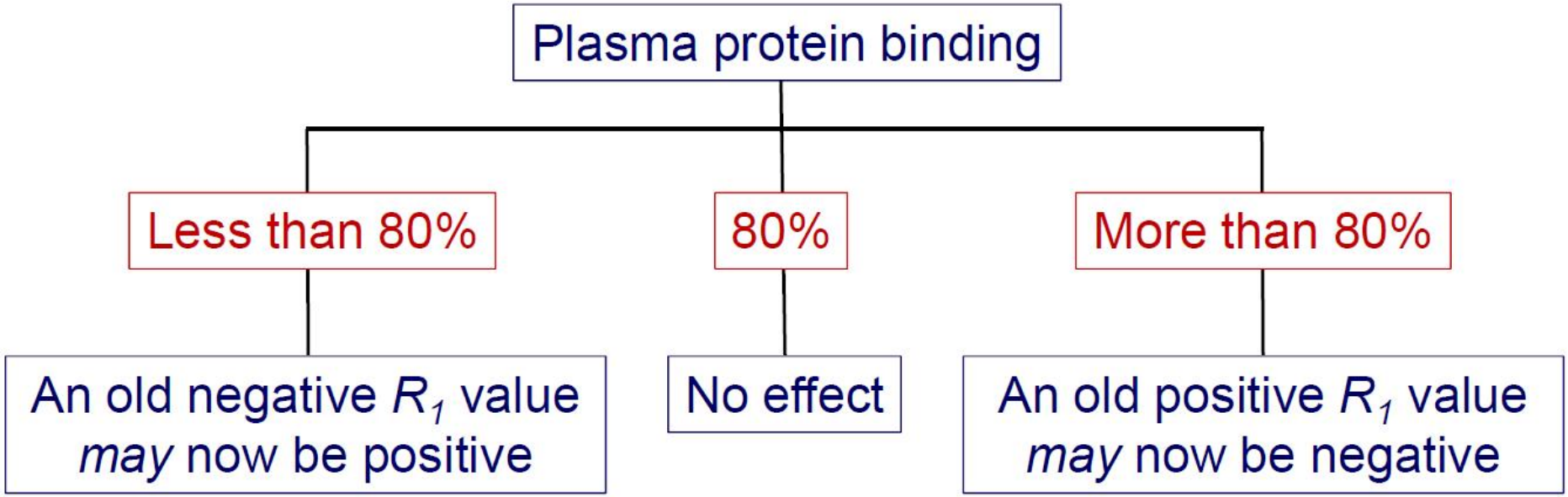
Agency	Date	Equation (as written)	Unbound or total concentration?	Cutoff for a positive result	Comment
FDA	2017	$R_1 = 1 + \frac{I_{max,u}}{K_i}$	Unbound C_{max} Unbound K_i	≥ 1.02	Same
PMDA	2017	$R = 1 + \frac{[I]}{K_i}$	Unbound C_{max} Not specified for K_i	≥ 1.02	Same
EMA	2013	$\frac{[I]}{K_i}$	Unbound C_{max} Not specified for K_i	≥ 0.02	Equivalent (it's missing the 1+ factor)

Reversible inhibition of **intestinal** CYP3A enzymes

Agency	Date	Equation (as written)	Concentration Nominal or unbound?	Cutoff for a positive result	Comment
FDA	2017	$R_{1,gut} = 1 + \frac{I_{gut}}{K_i}$	Dose/250 mL Unbound K_i	≥ 11	Same
PMDA	2017	$R = 1 + \frac{I_g}{K_i}$	Dose/250 mL Not specified for K_i	≥ 11	Same
EMA	2013	$\frac{[I]}{K_i}$	Dose/250 mL Not specified for K_i	≥ 10	Equivalent (it's missing the 1+ factor)

Reversible CYP Inhibition interpretation

Impact of plasma protein binding on old R1 values



Irreversible inhibition - Scope

Agency	Date	Scope – CYP enzymes	Other drug-metabolizing enzymes (DMEs)
FDA	2017	CYP1A2, 2B6, 2C9, 2C8, 2C9, 2C19, 2D6, and CYP3A (with 2 substrates)	None
PMDA	2017	CYP1A2, 2B6, 2C9, 2C8, 2C9, 2C19, 2D6, and CYP3A (with 2 substrates)	None
EMA	2013	CYP1A2, 2B6, 2C9, 2C8, 2C9, 2C19, 2D6, and CYP3A (with 2 substrates)	None

Guidance for in vitro studies – Perpetrator potential

Irreversible inhibition of **hepatic** CYP enzymes

Agency	Equation (as written)	Unbound or total concentration?	Cutoff $\frac{K_{obs} + K_{deg}}{K_{deg}}$	Comment
FDA (2017)	$K_{obs} = \frac{k_{inact} \cdot 50 \cdot I_{max,u}}{K_I + 50 \cdot I_{max,u}}$	Unbound C_{max} Not specified for K_I	≥ 1.25	Same
PMDA (2017)	$K_{obs} = \frac{k_{inact} \cdot 50 \cdot [I]}{K_I + 50 \cdot [I]}$	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

The FDA/PMDA (2017) equation is more conservative than the EMA's (2013)

Guidance for in vitro studies – Perpetrator potential

Irreversible inhibition of **intestinal** CYP enzymes

Agency	Equation	Unbound or total concentration?	Cutoff $\frac{K_{obs} + K_{deg}}{K_{deg}}$	Comment
FDA (2017)	There isn't one			Where's the formula?
PMDA (2017)	$K_{obs} = \frac{k_{inact} \cdot 0.1 \cdot [I]_g}{K_I + 0.1 \cdot [I]_g}$	$[I]_g$ = dose/250 mL Not specified for K_I	≥ 1.25	
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

The EMA (2013) equation is more conservative than the PMDA's (2017)

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CYP Induction scope

CYP1A2, 2B6 and 3A4 (first) plus (if positive) CYP2C8, 2C9, and 2C19 based on mRNA and/or activity (preferably mRNA)

Test system

- Human hepatocytes (n = 3)
- Treat with test drug for 48 or 72 h

New recommendation

- Measure test drug concentration in medium throughout the last day of treatment (similar to EMA 2013)

Caution

CYP2C19 *activity* is inducible, CYP2C19 *mRNA* is not

Yajima et al. Drug Metab Dispos. 42: 867-871, 2014

CYP Induction interpretation

The clinical relevance of *in vitro* induction data can be assessed by 4 basic methods:

1. Fold induction (> 2 fold) and % of positive control (>20%)
2. Relative induction score (RIS) with qualified hepatocytes/data
3. Ratio of $I_{max,u}/EC_{50}$ with qualified hepatocytes/data
4. R_3

$$RIS = \left(\frac{E_{max} \cdot I_{max,u}}{EC_{50} + I_{max,u}}\right)$$

$$R_3 = \frac{1}{1 + d \cdot \left(\frac{E_{max} \cdot 10 \cdot I_{max,u}}{EC_{50} + 10 \cdot I_{max,u}}\right)}$$

Induction – Equations and cutoffs

Agency	Equation (as written)	Measure *in vitro* concentration of test drug?	Cutoff for a positive result	Comment
FDA 2017	$R_3 = \frac{1}{1 + d \cdot \left(\frac{E_{max} \cdot 10 \cdot I_{max,u}}{EC_{50} + 10 \cdot I_{max,u}}\right)}$	Yes	≤ 0.8	Same
PMDA 2017	$R = \frac{1}{1 + d \cdot \left(\frac{E_{max} \cdot 10 \cdot [I]}{EC_{50} + 10 \cdot [I]}\right)}$	Yes [I] = $I_{max,u}$	≤ 0.8	Same
EMA 2013	The EMA describe 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 [I] = $I_{u,inlet.max}$	Not specified	

E_{max} is the maximum induction effect relative to control = 0, not 1 (= fold induction – 1)

Transporter inhibition scope

Agency	Date	Scope – Transporters	Comment
FDA	2017	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 (NEW)	Examine TDI of OATPs
PMDA	2017	Same (n = 9)	Same
EMA	2013	Same + OCT1 (hepatic uptake) and BSEP (hepatic efflux) (n = 11)	

P-gp and BCRP inhibition – Equations and cutoffs

Agency	Date	Equation (as written)	*In vivo* concentration Nominal or unbound *in vitro* concentration?	Cutoff for a positive result	Comment
FDA	2017	$\frac{I_{gut}}{IC_{50}}$	Dose/250 mL Not specified	≥ 10	Same
PMDA	2017	$\frac{I}{IC_{50}}$	Dose/250 mL Not specified	≥ 10	Same
EMA	2013	$\frac{0.1 \cdot Dose/250mL}{K_i}$	0.1 x Dose/250 mL Not specified	>1 Cutoff is 10 if Dose/250 mL is used	"Same"

Guidance for in vitro studies – Perpetrator potential

OATP1B1 and 1B3 inhibition – Equations and cutoffs

Agency	Equation (as written)	*In vivo* concentration Nominal or unbound *in vitro* concentration?	Cutoff for a positive result	Comment
FDA 2017	$R = 1 + \frac{fu_P \cdot I_{in,max}}{IC_{50}}$	Unbound inlet Not specified	≥ 1.1	R_b used in $I_{in.max}$ equation
PMDA 2017	$1 + \frac{f_u \cdot I_{inlet,max}}{K_i}$	Unbound inlet Not specified	≥ 1.1	R_b not used in $I_{in.max}$ equation
EMA 2013	$\frac{25 \cdot Imax_{u,inlet}}{K_i}$	Unbound inlet Not specified	>1	Equivalent cutoff is 1.04

FDA/PMDA now recommend a 30-min pre-incubation with OATPs

The current EMA cutoff (from 2013) is the lowest for hepatic uptake transporters

Guidance for in vitro studies – Perpetrator potential

OAT1, OAT3 and OCT2 inhibition – Equations and cutoffs

Agency	Equation (as written)	*In vivo* concentration Nominal or unbound *in vitro* concentration?	Cutoff for a positive result	Comment
FDA 2017	$\frac{I_{max,u}}{IC_{50}}$	Unbound plasma $C_{max,ss}$ Not specified	≥ 0.1	
PMDA 2017	$1 + \frac{unbound\ C_{max}}{K_i\ (IC_{50})}$	Unbound plasma $C_{max,ss}$ Not specified	≥ 1.1	Equivalent to FDA cutoff
EMA 2013	$\frac{50 \cdot Cmax_u}{K_i}$	Unbound plasma $C_{max,ss}$ Not specified	>1	Equivalent to a cutoff of 0.02

The current EMA cutoff (from 2013) is the lowest cutoff for renal uptake transporters

Guidance for in vitro studies – Perpetrator potential

MATE1 and MATE2-K inhibition – Equations and cutoffs

Agency	Equation (as written)	*In vivo* concentration Nominal or unbound *in vitro* concentration?	Cutoff for a positive result	Comment
FDA 2017	$\frac{I_{max,u}}{IC_{50}}$	Unbound plasma $C_{max,ss}$ Not specified	≥ 0.02	Cutoff is lower than for renal uptake transporters
PMDA 2017	$1+\frac{unbound\ C_{max}}{K_i\ (IC_{50})}$	Unbound plasma $C_{max,ss}$ Not specified	≥ 1.02	Equivalent to FDA cutoff
EMA 2013	$\frac{50 \cdot Cmax_u}{K_i}$	Unbound plasma $C_{max,ss}$ Not specified	>1	Equivalent to FDA cutoff of 0.02

The cutoffs are the same (equivalent) for all agencies

Guidance for in vitro studies – Perpetrator potential

Selected conservative (global) target *in vitro* concentrations

Assay type	Minimum target *in vitro* concentrations
Reversible CYP (or transporter) inhibition	To reach unbound IC_{50} ([S] = K_m): $100\ x\ \frac{I_{max.u}}{fu_{inc}}$
	To reach unbound IC_{90} ([S] = K_m): $1{,}000\ x\ \frac{I_{max.u}}{fu_{inc}}$
Reversible intestinal CYP3A, P-gp or BCRP inhibition	To reach unbound IC_{50} ([S] = K_m): $0.2\ x\ \frac{I_{gut}}{fu_{inc}}$
	To reach unbound IC_{90} ([S] = K_m): $2\ x\ \frac{I_{gut}}{fu_{inc}}$
CYP Induction	Limit of aqueous solubility and / or cytotoxicity

If unbound plasma C_{max} or dose not known: limit of aqueous solubility or cytotoxicity

Conclusions

- Depending on development stage and timeline:
  - Re-interpret existing data based on new cutoff criteria
  - Perform additional *in vitro* studies if needed for NDAs
- Harmonization:
  - 2017 FDA and PMDA guidances often match EMA 2013
- When PMDA differs from FDA:
  - Still seems to match the 2013 EMA guidance
  - Several examples in cutoffs, use of unbound conc.

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Comments or Questions?

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