Comparison Between the New US FDA and Japan PMDA In Vitro DDI Guidance Documents: Are We Close to Harmonization?

Brian W. Ogilvie[1] and Andrew Parkinson[2]

[1] XenoTech, LLC, 1101 W. Cambridge Circle Dr., Kansas City, KS, USA and [2]XPD Consulting, Shawnee, KS, USA

Abstract

What is already known about this subject?
- The US FDA and Japan PMDA released draft guidance documents on the subject of in vitro drug-drug interaction (DDI) studies in 2017
- Meetings were held between FDA, PMDA and the EMA prior to the release of the documents in an attempt to reach harmonization.

What this poster adds:
- Highlights of the similarities and differences between the 2017 FDA and PMDA draft *in vitro* DDI guidance documents
- A comparison with the 2013 EMA DDI guideline

Abstract:
In September, 2017, the Japan PMDA revised its 2014 guideline and released it (only in Japanese) for comments. In October, 2017, the US FDA revised and split its 2012 draft guidance for industry on in vitro drug-drug interaction (DDI) studies, into one document for in vitro DDI studies, and another for clinical DDI studies. An overview of the major changes, a comparison of each agency's equations and cut-off values, and a comparison of experimental details will be highlighted. This poster will also highlight strategies to harmonize the design of in vitro DDI studies to meet the expectations of both agencies.

Aims: 1) To highlight the major changes in the 2017 DDI guidance documents.
2) To compare and contrast the agencies' suggested experimental designs, equations and cut-off values.

Conclusion: The poster provides guidance for strategies on harmonizing the design of in vitro DDI studies to meet the expectations of the US FDA and Japan PMDA.

Highlights of Major changes – Victim Potential

Table 1: Timing of in vitro studies:

Study Type	FDA	PMDA
Victim: Metabolite ID and phenotyping	*Before* phase I	
Victim: P-gp & BCRP substrate potential	*Before* phase I	
Victim: Other transporter substrate potential	Early as possible based on routes of elimination	
Perpetrator: CYP inhibition & induction	*Implied* before phase I	*Before* phase I
Perpetrator: Transporters	*Before* phase I	

Timing was covered for some studies in 2013 EMA

FDA ". . . collect enough DDI information to prevent patients from being unnecessarily excluded . . ."

Table 2: 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

Additions relative to FDA 2017 in red

Table 3: 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 biliary 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
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.	

*FDA notes "most investigational drugs": not BCS1
PMDA: Other transporters to consider include OCT1 and MRP2

Table 4: Transporters – Simplified 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

- If positive, FDA says to consider clinical studies based on safety margin, likely co-medications, etc. & refers to the clinical DDI guidance and website
- PMDA is more nuanced:
  - P-gp: consider GI absorption, brain distribution and risk of CNS toxicity and renal secretion
    - If substrate $F_a F_g$ 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
  - Other transporters: clinically relevant inhibitors listed in guideline

Highlights of Major changes – Perpetrator Potential

Table 5: Drug metabolizing enzyme inhibition - Scope

Agency	Date	Scope – CYP enzymes (direct & irreversible)	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

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

Table 6: Interpretation of 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)

Table 7: Interpretation of 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)

Table 8: 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
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

Table 9: Interpretation of irreversible inhibition of intestinal CYP3A enzymes

Agency	Equation	Unbound or total concentration?	Cutoff $\frac{K_{obs} + K_{deg}}{K_{deg}}$	Comment
FDA (2017)	There isn't one			Use PMDA
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

Table 10: Interpretation of CYP Induction data

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	

Scope: CYP1A2, 2B6 and 3A4 mRNA OR activity. CYP2Cs if positive for CYP3A4.
Other basic models are available.
$I_{max,u}$ is unbound plasma $C_{max,ss}$
E_{max} is the maximum induction effect relative to control = 0, not 1 (= fold induction – 1)
EC_{50} is the measured *in vitro* concentration causing half-maximum induction
d is a scaling factor (assumed to be 1 for the basic static model)

Table 11: 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)	TDI of OATPs
PMDA	2017	Same (n = 9)	Same
EMA	2013	Same + OCT1 (hepatic uptake) and BSEP (hepatic efflux) (n = 11)	

FDA recommendation: Use *in vivo* index (probe) substrates for *in vitro* assays (due to substrate-dependent inhibition)

Table 12: 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"

Table 13: OATP1B1 and OATP1B3 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

Table 14: OAT1, OAT3, OCT2 (and MATEs*) 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 FDA cutoff of 0.02

* MATE1 and MATE2-K: as above, except cutoff values are ≥ 0.02 or ≥ 1.02 for FDA and PMDA, respectively.

Table 15: 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

- 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
- Due to the requirement for earlier in vitro DDI data, concentration ranges in experiments may need to be based on limits of solubility and / or cytotoxicity rather than C_{max}, maximum hepatic inlet concentration, or dose.

References

FDA 2017 Draft *in vitro* DDI Guidance (Link)
PMDA 2017 Draft *in vitro* DDI Guideline (Link - English)
EMA 2013 Final Guideline on the Investigation of Drug Interactions (Link)

XENOTECH
A BioIVT Company

XPD CONSULTING