# 2024 ICH M12 DDI Guideline
## Comparison with 2018 PMDA Guideline

**Cyprotex has prepared this simple summary to compare the ICH M12 Harmonized Guideline on Drug Interaction Studies (2024) with the Japanese PMDA Guideline on Drug Interaction for Drug Development (2018)**

### Reaction Phenotyping
- The ICH M12 references a larger range of Phase 2 enzymes if the investigational drug is not metabolised by the main CYP enzymes whereas the PMDA 2018 guideline suggests only evaluating UGT enzymes for Phase 2 metabolism.

### Enzyme Inhibition
- Risk of time dependent inhibition:
  - 5 x $C_{max,u}$ is used in the calculation for the ICH M12 whereas 50 x $C_{max,u}$ is used in the PMDA 2018 guideline.
  - PMDA 2018 has separate cut-offs for intestinal enzymes for orally administered drugs as well as systemic enzymes whereas the ICH M12 has the same cut-off for both.
- Both guidelines suggest investigating reversible UGT inhibition if direct glucuronidation is one of the major elimination pathways of the investigational drug but the ICH M12 references a larger panel of UGT isoforms.

### Enzyme Induction
- No major differences between the ICH M12 and PMDA guidelines.

### Transport Substrate
- No major differences between the ICH M12 and PMDA guidelines.

### Transport Inhibition
- In the ICH M12, the guideline considers both the oral and parenteral route for inhibition of P-gp and BCRP with different equations and cut-off values whereas the PMDA guideline only considers the oral route for these transporters.

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| *In Vitro* Assay | ICH M12 2024 | PMDA 2018 |
|---|---|---|
| **Reaction Phenotyping** | ***Main CYPs initially:***<br>• CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A<br>***If not main CYPs:***<br>• Non-CYP: AO, CES, MAO, FMO, XO, ADH/ALDH<br>• Phase 2: UGTs, SULTs, GSTs, NATs<br>• Other CYPs: CYP2A6, 2J2, 4F2, 2E1<br>***Decision***<br>Clinical study if metabolic pathway is ≥ 25% total elimination for metabolic pathway. | ***Main CYPs initially:***<br>• CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A<br>***If not main CYPs:***<br>• Non-CYP: AO, MAO, FMO, XO, ADH/ALDH<br>• Phase 2: UGTs<br>• Other CYPs: CYP2A6, 2J2, 4F2, 2E1<br>***Decision***<br>Clinical study if metabolic pathway is ≥ 25% total elimination for metabolic pathway. |
| **Enzyme Inhibition** | ***Main CYPs assessed (Reversible & TDI):***<br>• CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A (2 substrates)<br>***UGTs assessed (Reversible):***<br>• UGT1A1, 1A4, 1A9, 2B7, 2B15 if direct glucuronidation of test drug<br>***Decision (Reversible, non-oral, CYP & UGT)***<br>Clinical study excluded if $C_{max,u}/K_{i,u} < 0.02$<br>***Decision (Reversible, oral, CYP)***<br>Clinical study excluded if (Dose/250mL)/$K_{i,u} < 10$<br>***Decision (Time dependent, CYP)***<br>Clinical study or other models if $(k_{obs}+k_{deg})/k_{deg} < 1.25$, where $k_{obs} = (k_{inact} x 5 x C_{max,u})/(K_{i,u}+5 x C_{max,u})$ | ***Main CYPs assessed (Reversible & TDI):***<br>• CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A (2 substrates)<br>***UGTs assessed (Reversible):***<br>• UGT1A1, 2B7 if direct glucuronidation of test drug<br>***Decision (Reversible, non-oral)***<br>Clinical study excluded if $C_{max,u}/K_{i,u} < 0.02$<br>***Decision (Reversible, oral)***<br>Clinical study excluded if (Dose/250mL)/$K_i < 10$<br>***Decision (Time dependent, non-oral)***<br>Clinical study or other models if $(k_{obs}+k_{deg})/k_{deg} < 1.25$, where $k_{obs} = (k_{inact} x 50 x C_{max,u})/(K_{i,u}+50 x C_{max,u})$<br>***Decision (Time dependent, oral)***<br>Clinical study or other models if $(k_{obs}+k_{deg})/k_{deg} < 1.25$, where $k_{obs} = (k_{inact} x 0.1 x (Dose/250mL))/(K_i+0.1 x (Dose/250mL))$ |
| **Enzyme Induction** | ***Main CYPs assessed:***<br>• CYP1A2, 2B6, 3A4<br>***Other CYPs assessed:***<br>• CYP2C8. 2C9, 2C19 if CYP3A4 induction observed<br>***Decision (Basic mRNA fold change)***<br>Clinical study cannot be excluded if:<br>• mRNA expression increases in concentration dependent manner, and fold change is ≥ 2 at ≤ 50 x $C_{max,u}$, or<br>• fold change is < 2 but > 20% of the positive control response<br>***Decision (Correlation Methods)***<br>Clinical study excluded if AUC ratio > 0.8 where RIS = $(E_{max} \times C_{max,u})/(EC_{50,u}+C_{max,u})$, or $C_{max,u}/EC_{50,u}$<br>***Decision (Basic Kinetic Model)***<br>Clinical study excluded if R > 0.8 where $R = 1/(1+d \times E_{max} \times 10 \times C_{max,u}/(EC_{50,u}+10 \times C_{max,u}))$ | ***Main CYPs assessed:***<br>• CYP1A2, 2B6, 3A4<br>***Other CYPs assessed:***<br>• CYP2C8. 2C9, 2C19 if CYP3A4 induction observed<br>***Decision (Basic mRNA fold change)***<br>Clinical study cannot be excluded if:<br>• mRNA expression increases in concentration dependent manner, and fold change is ≥ 2 at ≤ 50 x $C_{max,u}$ or 0.1 x Dose/250ml<br>• fold change is < 2 but > 20% of the positive control response<br>***Decision (Correlation Methods)***<br>Clinical study excluded using pre-determined cut-off based on experience: RIS = $(E_{max} \times C_{max,u})/(EC_{50}+C_{max,u})$, or $C_{max,u}/EC_{50}$<br>***Decision (Basic Kinetic Model)***<br>Clinical study excluded if R > 0.8 where $R = 1/[1+d \times ((E_{max} \times 10 \times C_{max,u})/(EC_{50}+10 \times C_{max,u}))]$ |
| **Transporter Substrate** | ***Efflux transporters assessed:***<br>• P-gp & BCRP if test drug is administered orally or if biliary or active renal secretion are major elimination pathways<br>***Uptake transporters assessed:***<br>• OAT1B1/1B3 if hepatic metabolism or biliary excretion is ≥ 25% elimination or if pharmacological target in liver<br>• OAT1/3, OCT2, MATE1/2-K if active renal secretion is ≥ 25% systemic clearance<br>***Decision (Bidirectional Studies e.g., P-gp or BRCP)***<br>Clinical study considered if net flux ratio or efflux ratio is ≥ 2 and is inhibited by > 50% by known inhibitor of transporter<br>***Decision (Transporter expressed cells e.g., OATP1B1/1B3, OAT1/3, OCT2, MATE1/2-K)***<br>Clinical study considered if uptake in transporter expressed cells is ≥ 2-fold of empty vector cells and is inhibited by > 50% by known inhibitor of transporter | ***Efflux transporters assessed:***<br>• P-gp & BCRP<br>***Uptake transporters assessed:***<br>• OATP1B1/1B3 if hepatic metabolism or biliary excretion is ≥ 25% total clearance<br>• OAT1/3, OCT2, MATE1/2-K if active renal secretion is ≥ 25% of total clearance<br>***Decision (Bidirectional Studies e.g., P-gp or BRCP)***<br>Clinical study considered if net flux ratio or efflux ratio is ≥ 2 and is significantly inhibited by known inhibitor of transporter<br>***Decision (Transporter expressed cells e.g., OATP1B1/1B3, OAT1/3, OCT2, MATE1/2-K)***<br>Clinical study considered if uptake in transporter expressed cells is ≥ 2-fold of empty vector cells and is inhibited by known inhibitor of transporter |
| **Transporter Inhibition** | ***Main transporters assessed:***<br>• P-gp, BCRP, OATP1B1/1B3, OAT1/3, OCT2, MATE1/2-K<br>***Decision (P-gp or BCRP via oral route):***<br>Clinical study can be excluded if (Dose/250mL)/$IC_{50,u} < 10$<br>***Decision (P-gp or BCRP via parenteral route or metabolite formed post-absorption)***<br>Clinical study can be excluded if $C_{max,u}/IC_{50,u} < 0.02$<br>***Decision (OATP1B1/1B3)***<br>Clinical study can be excluded if $C_{max,inlet,u}/IC_{50,u} < 0.1$<br>***Decision (OAT1/3 and OCT2)***<br>Clinical study can be excluded if $C_{max,u}/IC_{50,u} < 0.1$<br>***Decision (MATE1/2-K)***<br>Clinical study can be excluded if $C_{max,u}/IC_{50,u} < 0.02$ | ***Main transporters assessed:***<br>• P-gp, BCRP, OATP1B1/1B3, OAT1/3, OCT2, MATE1/2-K<br>***Decision (P-gp or BCRP via oral route):***<br>Clinical study can be excluded if (Dose/250mL)/$IC_{50} < 10$<br>***Decision (OATP1B1/1B3)***<br>Clinical study can be excluded if $C_{max,inlet,u}/K_i < 0.1$<br>***Decision (OAT1/3, OCT2)***<br>Clinical study can be excluded if $C_{max,u}/K_i < 0.1$<br>***Decision (MATE1/2-K)***<br>Clinical study can be excluded if $C_{max,u}/K_i < 0.02$ |


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