2024 ICH M12 DDI Guideline
Comparison with 2013 EMA Guideline

Cyprotex has prepared this simple summary to compare the ICH M12 Harmonized Guideline on Drug Interaction Studies (2024) with the EMA Guideline on the Investigation of Drug interactions (2013)

Reaction Phenotyping
- No major differences exist between ICH M12 and the EMA 2013, however, the ICH M12 provides a longer and more specific list of enzymes to potentially assess.

Enzyme Inhibition
- No major differences between ICH M12 and EMA 2013 for assessment of reversible inhibition
- Risk of time dependent inhibition:
  - 5 x $C_{max,u}$ is used in the calculation for the ICH M12 whereas 1 x $C_{max,u}$ is used in the EMA 2013.
  - EMA 2013 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
- ICH M12 and the EMA 2013 guidelines are similar in terms of enzyme induction, however, the ICH M12 guideline provides more clarity on how to interpret the correlation and kinetic models.

Transport Substrate
- No major differences between the ICH M12 and EMA 2013 guidelines. However, the ICH M12 guideline provides more clarity on the interpretation of the results especially in the case of the uptake transporters.

Transport Inhibition
- The EMA 2013 guideline recommends screening for OCT1 and BSEP inhibition in addition to P-gp, BCRP, OATP1B1/1B3, OAT1/3, OCT2 and MATE1/2-K. These two transporters are not on the standard list for the ICH M12 but it is suggested that they may be assessed on a case-by-case basis with other transporters such as OATP2B1 and MRP2.
- The cut-off values differ between the two guidelines for certain transporters (OATP1B1/1B3, OAT1/3 and OCT2).
- The ICH M12 recommends a pre-incubation for transporters such as OATP1B1 and OATP1B3 whereas the EMA 2013 guideline does not refer to a pre-incubation as the scientific literature and consensus concerning this topic only started to appear later around 2017.

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In Vitro Assay	ICH M12 2024	EMA 2013
Reaction Phenotyping	***Main CYPs initially:*** • CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A ***If not main CYPs:*** • Non-CYP: AO, CES, MAO, FMO, XO, ADH/ALDH • Phase 2: UGTs, SULTs, GSTs, NATs • Other CYPs: CYP2A6, 2J2, 4F2, 2E1 ***Decision*** Clinical study if metabolic pathway is ≥ 25% total elimination for metabolic pathway.	***Main CYPs initially:*** • CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A ***If not main CYPs:*** • Non-CYP: ADH/ALDH etc • Phase 2: UGTs, SULTs, GSTs etc ***Decision*** Clinical study if metabolic pathway is ≥ 25% total elimination for metabolic pathway.
Enzyme Inhibition	***Main CYPs assessed (Reversible & TDI):*** • CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A (2 substrates) ***UGTs assessed (Reversible):*** • UGT1A1, 1A4, 1A9, 2B7, 2B15 if direct glucuronidation of test drug ***Decision (Reversible, non-oral, CYP & UGT)*** Clinical study excluded if $C_{max,u}/K_{I,u} < 0.02$ ***Decision (Reversible, oral, CYP)*** Clinical study excluded if (Dose/250mL)/$K_{I,u} < 10$ ***Decision (Time dependent, CYP)*** Clinical study or other models if $(k_{obs}+k_{deg})/k_{deg} < 1.25$, where $k_{obs} = (k_{inact} x 5 x C_{max,u})/(K_{I,u}+5xC_{max,u})$	***Main CYPs assessed (Reversible &TDI):*** • CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A (2 substrates) ***UGTs assessed (Reversible):*** • UGT1A1, 2B7 if direct glucuronidation of test drug ***Decision (Reversible, non-oral)*** Clinical study excluded if $C_{max,u}/K_I < 0.02$ ***Decision (Reversible, oral)*** Clinical study excluded if (Dose/250mL)/$K_I < 10$ ***Decision (Time dependent, non-oral)*** Clinical study or other models if $(k_{obs}+k_{deg})/k_{deg} < 1.25$, where $k_{obs} = (k_{inact} x C_{max,u})/(K_I+C_{max,u})$ ***Decision (Time dependent, oral)*** Clinical study or other models if $(k_{obs}+k_{deg})/k_{deg} < 1.25$, where $k_{obs} = (k_{inact} x (Dose/250mL))/(K_I+(Dose/250mL))$
Enzyme Induction	***Main CYPs assessed:*** • CYP1A2, 2B6, 3A4 ***Other CYPs assessed:*** • CYP2C8. 2C9, 2C19 if CYP3A4 induction observed ***Decision (Basic mRNA fold change)*** Clinical study cannot be excluded if: • mRNA expression increases in concentration dependent manner, and fold change is ≥ 2 at ≤ 50 x $C_{max,u}$, or • fold change is < 2 but > 20% of the positive control response ***Decision (Correlation Methods)*** Clinical study excluded if AUC ratio > 0.8 where RIS = $(E_{max} \times C_{max,u})/(EC_{50,u}+C_{max,u})$, or $C_{max,u}/EC_{50,u}$ ***Decision (Basic Kinetic Model)*** 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:*** • CYP1A2, 2B6, 3A4 ***Other CYPs assessed:*** • 2C9, 2C19 if CYP3A4 induction observed ***Decision (Basic mRNA fold change)*** Clinical study cannot be excluded if: • mRNA expression increases in concentration dependent manner, and fold change is ≥ 2 at ≤ 50 x $C_{max,u}$ or 0.1 x Dose/250mL, or • fold change is < 2 but > 20% of the positive control response ***Decision (Correlation Methods)*** Clinical study excluded if predefined cut-off reached where RIS = $(E_{max} \times C_{max,u})/(EC_{50}+C_{max,u})$ ***Decision (Mechanistic Static Model)*** Clinical study excluded if AUCR between 0.8 - 1.25
Transporter Substrate	***Efflux transporters assessed:*** • P-gp & BCRP if test drug is administered orally or if biliary or active renal secretion are major elimination pathways ***Uptake transporters assessed:*** • OAT1B1/1B3 if hepatic metabolism or biliary excretion is ≥ 25% elimination or if pharmacological target in liver • OAT1/3, OCT2, MATE1/2-K if active renal secretion is ≥ 25% systemic clearance ***Decision (Bidirectional Studies e.g., P-gp or BRCP)*** Clinical study considered if net flux ratio or efflux ratio is ≥ 2 and is inhibited by > 50% by known inhibitor of transporter ***Decision (Transporter expressed cells e.g., OATP1B1/1B3, OAT1/3, OCT2, MATE1/2-K)*** 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:*** • P-gp & BCRP ***Uptake transporters assessed:*** • OATP1B1/1B3 if hepatic metabolism or biliary excretion is ≥ 25% total clearance • OAT1/3, OCT2, MATE1/2-K if active renal secretion is ≥ 25% of total clearance ***Decision (Bidirectional Studies e.g., P-gp or BRCP)*** Clinical study considered if net flux ratio or efflux ratio is ≥ 2 ***Decision (Transporter expressed cells e.g., OATP1B1/1B3, OAT1/3, OCT2, MATE1/2-K)*** Clinical study considered if uptake in transporter expressed cells is observed
Transporter Inhibition	***Main transporters assessed:*** • P-gp, BCRP, OATP1B1/1B3, OAT1/3, OCT2, MATE1/2-K ***Decision (P-gp or BCRP via oral route):*** Clinical study can be excluded if (Dose/250mL)/$IC_{50,u} < 10$ ***Decision (P-gp or BCRP via parenteral route or metabolite formed post-absorption)*** Clinical study can be excluded if $C_{max,u}/IC_{50,u} < 0.02$ ***Decision (OATP1B1/1B3)*** Clinical study can be excluded if $C_{max,inlet,u}/IC_{50,u} < 0.1$ ***Decision (OAT1/3 and OCT2)*** Clinical study can be excluded if $C_{max,u}/IC_{50,u} < 0.1$ ***Decision (MATE1/2-K)*** Clinical study can be excluded if $C_{max,u}/IC_{50,u} < 0.02$	***Main transporters assessed:*** • P-gp, BCRP, OATP1B1/1B3, OAT1/3, OCT2, MATE1/2-K • OCT1 and BSEP may also be included ***Decision (P-gp or BCRP via oral route)*** Clinical study can be excluded if (Dose/250mL)/$K_I < 10$ ***Decision (P-gp or BCRP via parenteral route)*** Clinical study can be excluded if $C_{max,u}/K_I < 0.02$ ***Decision (OATP1B1/1B3)*** Clinical study can be excluded if $C_{max,inlet,u}/K_I < 0.04$ ***Decision (OAT1/3, OCT2, MATE1/2-K)*** Clinical study can be excluded if $C_{max,u}/K_I < 0.02$

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