2024 ICH M12 DDI Guideline
Comparison with 2020 FDA Guidance

Cyprotex has prepared this simple summary to compare the ICH M12 Harmonized Guideline on Drug Interaction Studies (2024) with the FDA In Vitro Drug Interaction Studies (2020).

Reaction Phenotyping

- In addition to the existing enzymes ICH M12 refers to additional Phase 2 enzymes including glutathione S-transferase and N-acetyl transferase.
- ICH M12 only recommends a single method for assessing the enzymes involved (human recominant enzymes or chemical inhibitors) whereas FDA 2020 recommends performing both methods.

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 FDA 2020.
- ICH M12 includes guidance on reversible UGT inhibition if direct glucuronidation is one of the major elimination pathways of the investigational drug.

Enzyme Induction

- ICH M12 recommends mRNA analysis (with exception of CYP2C19 where catalytic activity used) in human hepatocytes whereas the the FDA 2020 suggests either catalytic activity or mRNA is used in hepatocytes or immortalized hepatic cell lines.
- ICH M12 recommends cell viability is measured at start and end of incubation.
- Basic mRNA fold method: ICH M12 recommends testing up to a test drug concentration of 50 x $C_{max,u}$ whereas FDA 2020 only suggests testing up to 30 x $C_{max,u}$.
- ICH M12 refers to unbound EC_{50} ($EC_{50,u}$) in calculations for correlation methods and basic kinetic model whereas FDA 2020 only refers to EC_{50}.

Transport Substrate

- No major differences between the ICH M12 and FDA 2020.

Transport Inhibition

- P-gp and BCRP inhibition (parenteral route of administration or post-absorption metabolite formed): For ICH M12, 50 x $C_{max,u}$ has been used in the calculation whereas 10 x C_{max} has been used for the FDA 2020.
- MATE1 and MATE2-K inhibition: For ICH M12, 50 x $C_{max,u}$ has been used in the calculation whereas 10 x $C_{max,u}$ has been used for the FDA 2020.
- ICH M12 refers to unbound IC_{50} ($IC_{50,u}$) in calculations for transporter inhibition whereas FDA 2020 only refers to IC_{50}.

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Comparison with 2020 FDA Guidance

In Vitro Assay	ICH M12 2024	FDA 2020
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: AO, CES, MAO, FMO, XO, ADH/ALDH • Phase 2: UGTs, SULTs • Other CYPs: CYP2A6, 2J2, 4F2, 2E1 ***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) ***Decision (Reversible, non-oral)*** Clinical study excluded if $C_{max,u}/K_{I,u} < 0.02$ ***Decision (Reversible, oral)*** Clinical study excluded if (Dose/250mL)/$K_{I,u} < 10$ ***Decision (Time dependent, non-oral)*** Clinical study or other models if $(k_{obs}+k_{deg})/k_{deg} < 1.25$, where $k_{obs} = (k_{inact} x 50 x C_{max,u})/(K_{I,u}+50xC_{max,u})$
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:*** • 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 ≤ 30 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 = $(E_{max} \times C_{max,u})/(EC_{50}+C_{max,u})$, or $C_{max,u}/EC_{50}$ ***Decision (Basic Kinetic Model)*** Clinical study excluded if R > 0.8 where $R = 1/[1+d \times ((E_{max} \times 10 \times C_{max,u})/(EC_{50}+10 \times C_{max,u}))]$
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:*** • OATP1B1/1B3 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 and BCRP unless high permeable and high solubility drugs (exception if tissue safety concerns) ***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 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
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 ***Decision (P-gp or BCRP via oral route):*** Clinical study can be excluded if (Dose/250mL)/(K_I or IC_{50}) < 10 ***Decision (P-gp or BCRP via parenteral route):*** Clinical study can be excluded if $C_{max}/(K_I$ or $IC_{50}) < 0.1$ ***Decision (OATP1B1/1B3)*** Clinical study can be excluded if $C_{max,inlet,u}/IC_{50} < 0.1$ ***Decision (OAT1/3, OCT2, MATE1/2-K)*** Clinical study can be excluded if $C_{max,u}/IC_{50} < 0.1$

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