# ICH M12 Drug Interaction Final Guidance

## *Clinical DDI Assessments*

**Kellie Reynolds, Pharm.D.**
Director, Division of Infectious Disease Pharmacology
Office of Clinical Pharmacology (OCP)
Office of Translational Sciences (OTS)
CDER | FDA

October 9, 2024

# Outline

- Introduction/Goals
- Study types
- Studies for specific interaction mechanisms
  - CYP-mediated interactions
  - UGT-mediated interactions
  - Transporter-mediated interactions
- Endogenous biomarkers
- Nested DDI studies
- Interpretation of results
- Extrapolation of study results
- Predictive modeling
- Risk assessment and management
- Conclusions

# Drug Interaction Studies

## *Within the Context of a Drug Development Program*

From the background section of ICHM12:

"This guidance provides **general recommendations** on how to evaluate the DDI potential of an investigational drug. It is recognized that the DDI evaluation is **generally tailored** based on the **specific drug, intended patient population, and therapeutic context**. Alternative approaches may be acceptable if properly justified."

Thus, the scientific rigor described in the guidance needs to be considered with the patient population in mind. The end of the process is useful information for the health care provider and patient.

# Study goals

- Overarching goals of a clinical DDI study
  - Determine the presence or absence of a clinical DDI
  - Magnitude of the DDI if one exists
  - Outcome: assessment of the need for a DDI management strategy
- More nuanced purpose of various studies
  - Define the DDI liability via a specific pathway
  - Refine the understanding of DDIs in clinical use
  - Note- some studies may serve both purposes

# Study Types

| Study Type | Definition |
|---|---|
| **Standalone** | Primary objective is to determine presence or absence of a DDI and the magnitude of the DDI |
| **Nested** | Evaluates DDIs as part of larger studies in patients (e.g. Phase 2/3) for which DDI evaluation is not the primary objective |
| **Study with index precipitants or substrates** | Index drugs have well-understood and predicable properties regarding level of inhibition, induction, or metabolic pathway. Studies with these drugs typically define the greatest magnitude of interaction for the studied pathway. |
| **Study with expected concomitant drugs** | Investigates DDIs between the investigational drug and drugs likely to be administered in the target population |
| **Cocktail study** | Investigates the effect of the investigational drug on substrates for multiple enzymes and/or transporters |
| **Biomarker approach – NEW!!** | Approach that utilizes endogenous biomarkers that are substrates for drug metabolism and/or transport |

# Selecting substrates, inhibitors, inducers
# General considerations

- Consider the goal of the study
  - Studies with index precipitants and index substrates*
    - Estimate greatest magnitude of interaction
    - Extrapolate to other drug combinations
  - Studies with expected concomitant drugs
    - Often based on mechanistic understanding of DDI potential
    - Provide useful clinical information for a drug pair
    - May be difficult to extrapolate to other drugs

*Index precipitants and substrates (objects) are not available for transporters and UGT enzymes

# CYP-mediated DDIS

- Drug as CYP substrate
  - Typical- Start with a strong index inhibitor and strong index inducer
  - Some scenarios- starting with moderate inhibitor or inducer may be informative
  - Evaluation of polymorphic enzyme- PM vs EM evaluation may be appropriate (Effect of PM is expected to be similar to the effect of a strong inhibitor)
- Drug as CYP inhibitor or inducer
  - Start with a sensitive index substrate
  - Consider selectivity of index drug for the enzyme, to aid selection of substrate and interpretation of results

# UGT studies, following in vitro evaluation

- Drug as substrate of UGTs
  - case-by-case basis, considering the safety profile of the drug and the likelihood of its concomitant use with inhibitors of that UGT isoform
  - consider other enzymes/transporters involved with the drug's ADME
- Drug as inhibitor of UGTs
  - case-by-case basis, considering likelihood of the drug's administration with substrates and the safety profile of those substrates

# UGT studies, Drug as inducer of UGTs

- Limited understanding of gene expression of UGTs
- UGTs are co-regulated with CYP3A, by agonists of PXR and/or CAR, but are less inducible than CYP3A
- If drug reduces AUC of sensitive CYP3A substrate by >50%, clinical DDI study with UGT substrates should be considered (case-by-case)
  - Magnitude of CYP3A substrate decrease
  - Likelihood of use with UGT substrates
  - Are the UGT substrates also substrates for other enzymes/transporters regulated by PXR/CAR

# Transporter studies, following in vitro evaluation

Considerations for clinical evaluation of drug as substrate of transporters

| **Transporters** | **When a clinical DDI study should be considered** |
|---|---|
| P-gp and BCRP | When intestinal absorption is limited, or biliary excretion/active renal secretion is a major elimination pathway. |
| OATP1B1 and OATP1B3 | When hepatic (metabolic/biliary) elimination is a significant clearance pathway (≥25%) for the investigational drug or the action site of the drug is in liver, and the drug's properties support the importance of active uptake of the drug into the liver. |
| OAT1 and OAT3,<br>OCT2, MATE1, and MATE2-K | When the investigational drug undergoes significant active renal secretion (i.e., accounting for ≥ 25% of systemic clearance) |

# Drug as transporter substrate: clinical studies

- Selected precipitant drug should be a known inhibitor of the transporter under study
  - Lack of index inhibitors for transporters; inhibitor is generally selected based on likely concomitant use
  - M12 appendix includes examples (not a comprehensive list)
  - Consider other enzymes/transporters involved with the drug's ADME

# Drug as transporter inhibitor: clinical studies

- The need to conduct a clinical study is based on likely concomitant drugs and safety considerations
- Preferred substrate drugs (examples in M12 appendix)
  - Pharmacokinetic profile is markedly altered by coadministration of known inhibitors of the transporter
  - Likely concomitant drug
- Endogenous biomarker studies can be informative. (More information later in the presentation)

# Drug as transporter inducer: clinical studies

- M12 only mentions Pgp in the transporter induction section
- P-gp is co-regulated with CYP3A, by agonists of PXR and/or CAR, but is less inducible than CYP3A
- Thus, similar to considerations for UGT induction
  - If drug reduces AUC of sensitive CYP3A substrate by >50%, clinical DDI study with Pgp substrates should be considered (case-by-case)
    - Magnitude of CYP3A substrate decrease
    - Likelihood of use with Pgp substrates; exposure-response (efficacy)
    - Are the P-gp substrates also substrates for other enzymes/transporters regulated by PXR/CAR

# NEW! Endogenous Biomarker Studies- General

- Alternative approach to assess an investigational drug's potential as a precipitant: evaluating the change in exposure of a well-characterized endogenous substrate

- Sufficient analytical validation should be conducted

- Not all endogenous biomarkers are validated and characterized in terms of their performance characteristics (sensitivity, selectivity, specificity, dynamic range, correlation with pharmacokinetic parameters of the probe drugs, and variability)

# Plasma coproporphyrin I (CPI) for evaluation of hepatic OATP1B inhibition potential

Supported by recent literature reports

Can incorporate into early healthy volunteer PK studies

- Plasma CPI measured prior to drug administration = baseline concentration
- Baseline AUCt = baseline CPI x t
- Serial samples post drug administration allow characterization of Cmax and AUC of CPI
- Determine ratio (post drug administration/baseline) of CPI AUC and Cmax
- Ratio < 1.25 indicates low likelihood of clinical DDI via OATP1B inhibition

# Nested DDI Studies

DDIs are evaluated as part of a larger study in patients. The DDI evaluation should be prospectively planned.

Advantages

Relevant population

May represent anticipated clinical setting

Challenges

Study design and data collection

Typically evaluates investigational drug as object, not often as precipitant

# Nested DDI Studies- Design Considerations

- Prospective design and plan
  - Prespecify concomitant drugs to evaluate
  - Simulations can assist sampling times, number of samples
  - Data collection- time of drug administration, sampling, food intake, other concomitant drugs
  - Population PK analysis plan
- Unplanned (retrospective analysis)
  - Not ideal
  - May be conducted because of observed safety or efficacy issues or new DDI concerns
  - Utility depends on quality of data collected
  - DDIs identified or ruled out may need to be confirmed using a prospective evaluation

# Interpretation: Drug as Object

- Point estimate (ratio between the exposure of the object with and without the precipitant) can be used to describe the magnitude of the interaction.

- Use of No-Effect Boundaries

  Preferred Approach

  – Develop no-effect boundaries based on exposure-response relationship from clinical trials (efficacy and safety)
  – Consider variability of exposure in indicated population

  80 to 125% acceptance range

  – Mentioned in M12, but not preferred
  – Typically overly conservative

# Interpretation: Drug as Precipitant

- No change from classification system for CYPs (inhibitors and inducers: strong, moderate, weak)

- Currently- no classification system for non-CYP enzymes or transporters
  - Interacting mechanisms may involve other transporters and/or enzymes, making the establishment and use of a classification system challenging

# Extrapolation of Study Results

- Not possible to study all combinations of drugs
- Complex scenarios- interactions that involve multiple pathways or combine with organ impairment
- Knowledge of ADME properties (investigational drug; potential concomitant drugs) can assist extrapolation
- Mechanistic modeling can assist extrapolation

# Predictive Modeling

The predictive modeling appendix to ICH M12 indicates how mechanistic modeling approaches can be used to:

- characterize the potential for DDIs
- indicate whether a dedicated clinical DDI study is needed
- support clinical recommendations in the absence of a clinical DDI study

Multiple approaches for assessing DDI risk may be feasible

Any model used for quantitative prediction requires use of appropriate in vitro experimental conditions

# Predictive Modeling- Mechanistic Static

- Incorporate detailed drug disposition and DDI mechanisms for precipitant and object
  - May estimate the effect of several combined interaction processes
  - Input parameters should be justified by data and/or literature

- Most frequent use- investigational drug as precipitant of CYP interaction

- Current use- If AUCR (AUC ratio) is between 0.80 to 1.25, additional evaluation of drug as a perpetrator is not needed
  - When more relevant drug concentrations in gut and liver can be determined, mechanistic static models may provide quantitative estimates of DDIs

# Predictive Modeling- PBPK

- ICH M12 addresses utility of PBPK modeling for DDI evaluation and expectations specific to DDIs
- PBPK models can assist in the evaluation of the DDI potential of a drug and/or a metabolite as an object or precipitant of enzyme or transporter-mediated interactions
- When using PBPK modeling to support decisions, justify the following:
  - Model assumptions
  - Variability and uncertainty measures
  - Physiological and biological plausibility

# Risk Assessment and Management

Risk assessment should inform DDI management strategies

- DDI management = DDI prevention and risk minimization
- Strategies are needed when co-administration of drugs leads to concerns greater than when the drugs are administered alone

A few considerations

- Variability of observed DDI data
- Anticipated duration of concomitant use
- Medical need for the drugs, including alternatives
- Availability of monitoring parameters (therapeutic drug monitoring, laboratory tests)

# Risk Assessment and Management

Possible instructions for management:

- Change dose level or frequency
- Stagger administration
- Prohibit concomitant use
- Monitor concentration, lab results, signs, or symptoms (and possibly adjust dose)

*Note- The guidance does not provide specific language regarding instructions for DDI management. However, as we consider the strategies, it is essential to consider them from the perspective of the health care provider and patient. Can reasonable instructions be provided and followed?*

# Conclusions

- Tremendous advancements have been made enhancing our understanding of DDIs. Collective effort from industry, academia, and regulatory agencies led to global harmonization.
- The scientific rigor described in the guidance needs to be considered with the patient population in mind. The end of the process is useful information for the health care provider and patient.
- There are still areas that warrant further research, to improve the efficiency of DDI assessments during drug development.
  - Refine extrapolation of DDI results, including in complex scenarios
  - Additional endogenous biomarkers
  - Further utility of predictive modeling (mechanistic static and PBPK)

# Acknowledgements


- ICH M12 Expert Working Group

- Rajanikanth Madabushi (Rapporteur)
- Xinning Yang (Deputy Topic Lead)
- Helen Heymann (Rapporteur Supporter)
- Daphney Jean (previous Rapporteur Supporter)
- Sharonjit Sagoo (previous Rapporteur Supporter)
- Shiew Mei Huang
- Issam Zineh

- FDA/Office of Clinical Pharmacology internal group of experts (Donna Volpe, Vikram Arya, Elimika Fletcher, Wentao Fu, Joseph Grillo, Cindy (Liping) Pan, Anuradha Ramamoorthy, Mongthuong Tran, Manuela Grimstein, and Yuching Yang)

# CE Challenge Questions

# Challenge Question #1

**What are the most important drug metabolizing enzymes?**

a. Carboxylesterases (CES)

b. Cytochrome P450 (CYP) enzymes

c. Monoamine oxidase (MAO)

d. UDP glucuronosyl transferases (UGTs)

# Challenge Question #2

**A classification system for a drug as an inhibitor (strong, moderate, weak) or inducer (strong, moderate, weak) is available for which of the following drug interactions:**

a. Cytochrome P450 (CYP) enzyme mediated
b. UDP glucuronosyl transferases (UGTs) mediated
c. Drug transporter mediated
d. All of the above

# Thank you for attending today

## We will now answer more questions