Evaluation of New Chemical Entities as Victims of Metabolic Drug Drug Interactions

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IQ DDI Victim Working Group
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Victim(Affected Drug) DDI : The Issue

Victim DDI Risk Assessment is Critical for:

Early clinical risk assessment to guide ***Safe*** First in Human

- Certain exclusion criteria (DDI/Polymorphism)

Ensure Patient safety → drug development, registration, and post-marketing phases

Definitive studies not commonly done till POC/Ph2

Currently no recommended integrated strategy for victim DDI risk assessment in the clinic

FIH: First in Human; POC: Proof of Concept

Goal Of Working Group

Collaboration of 21 IQ companies to : Integrate existing best industry practices of use of in vitro methods, in vivo preclinical studies, modeling and simulation, to recommend strategy to evaluate NCEs to be *victim of metabolic DDIs* in the clinic → To be published as White Paper (Q4 2014)

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George Lai	Eisai, Inc.
Heidi Einolf	Novartis
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Jim Keirns	Astellas
Jennifer Yang	Incyte
Louis Leung	Pfizer
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Ralph Stearns	Vertex
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NCE: New Chemical Entity

Three Critical Areas of Focus of WG

De-risking Victim Drug DDI potential

- **f_{CL}**
  - **How best to estimate contribution of metabolism vs renal/biliary excretion to NCE CL**
  - **Perspective & Recommendations**
- **f_m**
  - **Guidelines to estimate *fractional contribution* of CYPs & non-CYPs towards NCE metabolism**
  - **Current status & future needs**

- **Modelling & Simulation (M&S)**
  - **Key input information for victim drug DDI prediction**
  - **Recommend M&S strategy to influence decision-making at different stages of drug development**

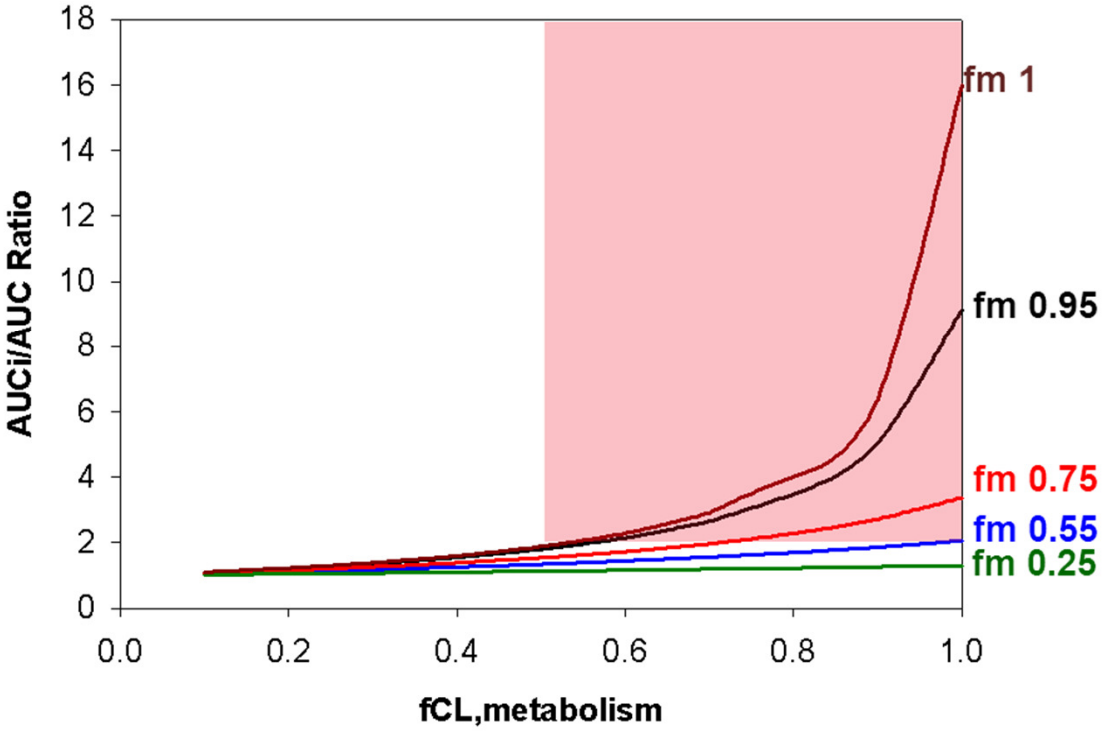
WG: Working Group; CL: Clearance; NCE: New Chemical Entity

f_{CL} and f_m

f_{CL} : Fraction of drug *cleared* by a pathway: Route of Clearance

$$f_{CL,metabolism} + f_{CL,renal} + f_{CL,biliary} = 1$$

f_m : Fraction of drug *metabolized* by an enzyme (i.e. $f_{m,\ CYP3A4}$)



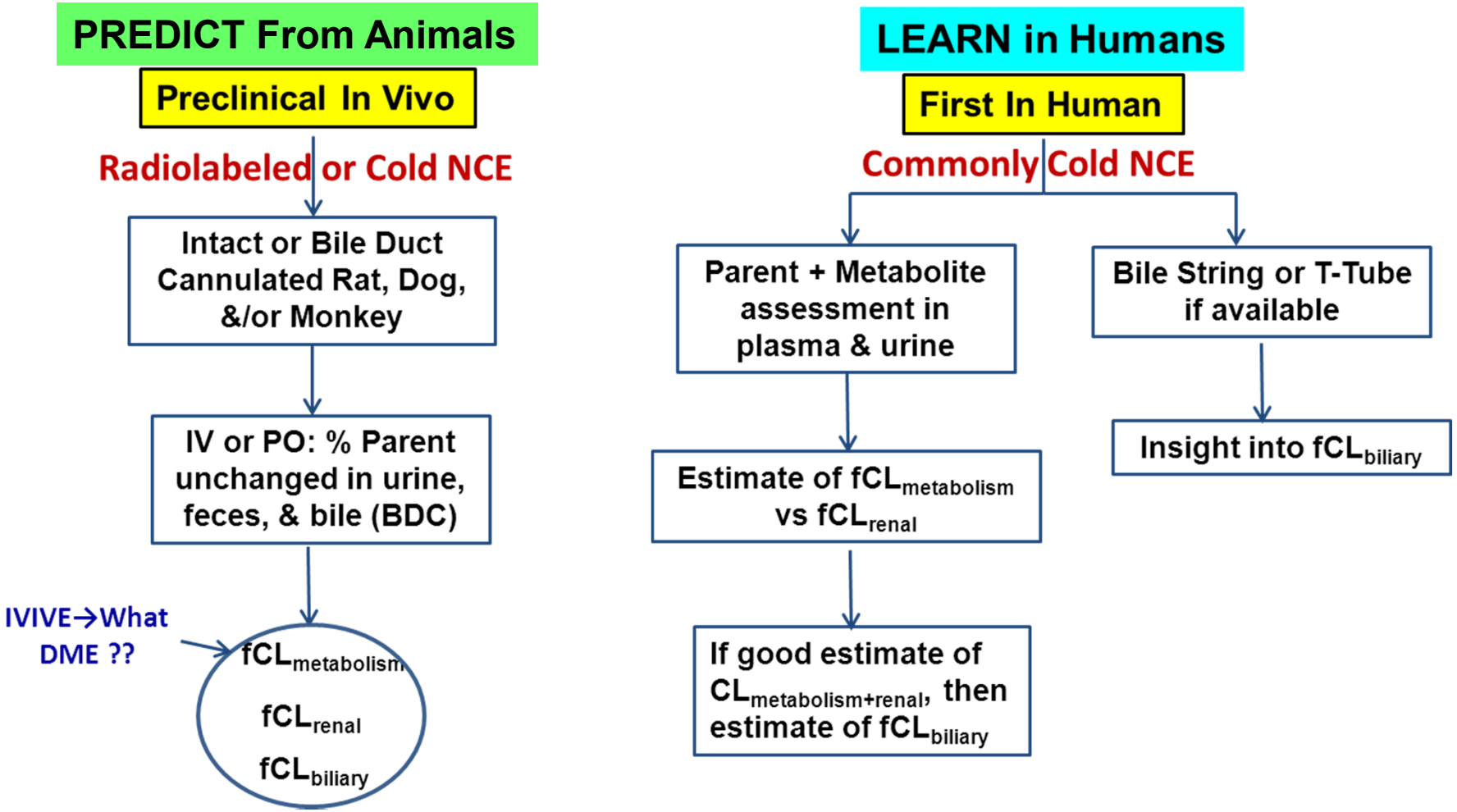
Potential severe ramifications when f_m x $f_{CL,metabolism}$ > 0.5

f_m and f_{CL} assessments commonly not done till Ph2

With Competitive inhibitor with [I]/Ki of 15
(Ref: Rowland Matin equn)

Approaches to Estimate f_{CL}

f_{CL} Estimation : Preclinical & in Humans



Understanding role of metabolism *in humans* is critical to making an accurate prediction of victim DDI potential

DME: Drug Metabolizing Enzyme; IVIVE: In Vitro In Vivo Extrapolation; IV: Intravenous; PO: Oral

f_{CL} Determination in Humans

CONFIRM

- **Clinical DDI study with CYP-selective (or appropriate DME) inhibitor**

$$f_{m,CYP} \approx f_{i,CYP} = 1-(AUC_{control}/AUC_{inhibited})$$

Shou et.al, DMD, 2008

-assumes complete inhibition of the CYP enzyme
- for CYP3A4, assumes $Fg_{inhibited} = Fg_{control}$

- **Radiolabeled human ADME study**

-$f_{CL,metabolism}$, $f_{CL,\ renal}$ quantitatively determined
-Elimination pathways defined (in excreta), e.g. metabolic, parent drug secretion, etc.

Caveats: unstable metabolites in excreta (e.g. glucuronides converted back to parent in feces), non-absorbed parent drug vs. secreted parent, estimations of enzyme involved in the primary reaction(s) when secondary/tertiary metabolites formed

F_G: Fraction escaping gut metabolism

Perspective From f_{CL} Approaches

The *sequence, timing, & nature of* a *common* set of in vitro & in vivo studies that companies routinely rely on, to estimate $f_{CL,metabolism}$ in humans depends on case by case approach.

In absence of definitive f_{CL} data in humans, thoroughly assess available information of NCE (BCS class, confidence in human IVIVE based on animal IVIVE, $f_{CLmetabolism}$ vs $f_{CLrenal/biliary}$ in animals, in vitro human transporter data) before risk assessment based on worst case scenario (assume $f_{CL,metabolism}$=1)

NCE: New Chemical Entity; BCS: Biopharmaceutical Classification System; IVIVE: In Vitro In Vivo Extrapolation

Estimating f_m In Vitro

Estimation of f_m

- Identify which metabolizing enzyme(s) involved
- Estimate " What is Fraction" metabolized by DME: f_m

Structure of NCE and Metabolite Profiling generally gives good idea of what to look for:

- Oxidative vs Direct Conjugation vs other metabolic pathways
- NADPH-dependent or not

When contribution by a metabolizing enzyme is **≥25%** then determine f_m

DME: Drug Metabolizing Enzyme

f_m Determination - Recommended Guidelines

- Identification of DME and f_m estimation in NCE metabolism most sensitive when monitoring major metabolite(s) formed
- Quantitative metabolite assessment best done with ^{14}C-NCE. When not available, 'relative' assessments can be made utilizing UV or LC/MS/MS
- When NCE has multiple metabolites, or ^{14}C NCE &/or metabolite standards not available, monitoring NCE disappearance has yielded reasonable success *(caveat: parent needs to be moderate to high CL)*
- Common approaches for f_m estimation: RAF/ISEF, selective enzyme inhibition (monitoring inhibitor cross-reactivity)

NCE: New Chemical Entity; DME: Drug Metabolizing Enzyme

f_m- Current Status : Quantitative or Qualitative ?

Enzyme	Tools available for RAF or ISEF			Chemical Inhibitors	fm (from in vitro studies)		Clinical Victim DDI Risk
	Recombinant Enzyme	Probe substrates	Tissue abundance		Overall Enzyme family	Individual Isoforms	(Reported example of victim drug)
CYP	Yes (various)	Yes[a]	Yes[a]	Yes[a]	Quantitative	Quantitative	High (Terfenadine, astemizole, cisapride)
FMO	Yes (1, 3, 5)	Yes[b]	Yes[c]	Yes[b]	Quantitative	Qualitative	Low
AO/XO	Emerging[d]	Yes	Emerging[d]	Yes	Quantitative	NA	Moderate (Allopurinol-XO)
MAO	Yes (A & B)	Yes	No	Yes	Quantitative	Qualitative	Low
UGT	Yes (Various)	Yes[e]	Emerging[f]	Yes[g]	Quantitative	Quantitative[g]	Moderate (Morphine, AZT, lorazepam, mycophenolate mofetil)
SULT	Yes (Various)	Yes[h]	Emerging[h]	Yes[b]	Quantitative[h]	Qualitative	Low
NAT	Yes (1 & 2)	Yes	No	Yes	Quantitative[i]	Qualitative	Moderate (Isoniazid)
GST	Yes(Various)	No	Yes[j]	Yes[b]	Qualitative	Qualitative	Low
CES	Yes (1 & 2)	Yes[j]	No	Yes	Qualitative	Qualitative	Low

a: For major isoforms
b: Non-isoform selective
c: mRNA –based abundance reported
d: In liver
e: For e.g. 1A1, 1A4, 1A6, 1A9, 2B7
f: For e.g. 1A1, 1A3, 1A4, 1A5, 1A6, 1A7, 1A8, 1A9, 1A10, 2B4, 2B7, 2B15, 2B17- liver, intestine, & kidney
g: For some isoforms – e.g. 1A1, 1A4, 1A6, 1A9, 2B7
h: For e.g. 1A1, 1A3/4, 1B1, 1E1, 2A1- Liver, intestine, kidney, lung (relative abundance)
i: Limited reports
j: Limited e.g GSTA1, A2, M1, M2, M3 and P1
k: UV & fluorescent probe metabolic pathways

High: Several Reported
Moderate : Few/Occassional Reported
Low: None Reported

Perspectives of f_m Approaches

Areas we feel confident in:

- Identification of DMEs involved
- $f_{m,CYP}$, $f_{m,UGT}$ (select)
- Contribution of CYP vs other oxidative DMEs when pathways overlap
- Contribution of Conjugative DMEs
    - semi-quantitative (cold NCE) or quantitative (radiolabeled NCE) metabolite profiling in vitro human matrices &/or Ph1 studies

Areas we are gaining confidence in:

-f_m non-CYP enzymes

- The "CYP" journey has helped demonstrate what we need- ***scaling*** of non-CYPs emerging
- Scaling of CYPs & non-CYPs in extrahepatic tissues
- f_m of low CL compounds

When quantitative f_m of a DME is not available, thoroughly assess known risk → incidence & magnitude of clinical DDI reported via that DME, before best/worst case scenario assumptions (e.g. $f_m \geq 0.5$)

DME: Drug Metabolizing Enzyme; NCE: New Chemical Entity

Modeling & Simulation in Victim Drug DDI Predictions

Models & Data Required Depends on Timing & Objective

Common Models Used
Simple Static
Mechanistic Static
Mechanistic Dynamic

Study/Data	Question to address/stage
In vitro human metabolism study –met ID and profile	Involvement of metabolic CL and CYP enzyme
Reaction phenotyping	Contribution of CYP in metabolic CL (f_m)
In silico & in vitro (logP, pKa, $f_{u,p}$, B/P, P_{app}, CL_{int} etc.)	Human PK (f_a, k_a, V_{ss}, CL) prediction
Preclinical mass balance study	Route(s) of CL
Clinical PK (oral)	Refine model and guide clinical DDI study design
Clinical PK (IV), human mass balance study	Disposition in human, estimate f_{mCYP}, F_G, f_a, F_{oral}, biliary or renal CL
Clinical DDI w/ strong inhibitor	confirm in vivo f_{mCYP}, predict other DDIs

Late /Discovery/Pre-FIH Clinical

M&S Recommendations

Select a fit-for-purpose model, based on specific application and stage of drug discovery/development

Utilize sensitivity analysis to help identify uncertainty & its impact on DDI risk assessment thoroughly

- Recommend additional key experimental data
- Common parameters for sensitivity analysis: $f_{mCYP,}$ $f_{u,gut}$ /F_g

Consider other factors when leveraging DDI predictions for decision-making and clinical study plan (i.e. safety margin of victim drugs, co-meds, special populations & dose regimens)

Modelling *is only as good as data provided so use caution with parameters & approximations to avoid poor & misleading outcomes*

Integrated Strategy of Victim DDI Assessment

Majority of NCEs have the potential to be a victim of some DDI since they all have to be cleared by some pathway

Preclinical Development

Victim DDI risk assessment should be made at all stages with focus on f_{CL}, f_m, M&S

- Make best estimate of $f_{CL,metabolism/renal/(biliary)}$ (preclinical in vivo & IVIVE) & f_m(in vitro)
- Integrate all data via M&S for worst case scenario with assumption that all metabolism by major enzyme(s) identified in vitro
  - Informs whether clinical exclusion required (DDI/polymorphism) in FIH
  - Guides Safe Starting Dose for Victim DDI Study in Clinic

Clinical Development

- Learn any additional information to refine DDI predictions from FIH studies
- Determine $f_{CL,metabolism/renal/(biliary)}$ → ^{14}C-Human ADME study
- Determine f_m → Clinical Victim DDI Study
- Refine DDI model to predict additional DDIs
- Support dose selection, labelling, justification of delay/waiver of clinical DDI studies