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EMA Perspectives on Regulatory Guidance on Drug-drug Interaction

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Disclaimer

The views expressed in this presentation are the personal views of the speaker and may not be understood or quoted as being made on behalf of or reflecting the position of the EMA , the Swedish Medical Products Agency or ICH M12.

Outline

- EMA guideline on the investigation of drug interactions
- QA and ongoing update of EMA GL, ICHM12
- PBPK reporting guideline

History and future of the European DDI guideline

- 1998 first guideline into operation
- 2013 updated version into operation
- 2014→ QA are published on the EMA website
- 2017 concept paper released on a planned update

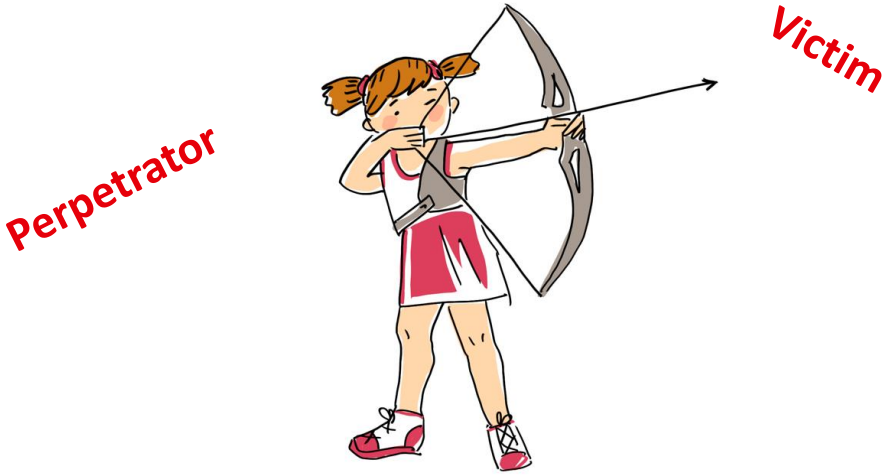
- Further update is awaiting ICH M12 work

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 June 2012
CPMP/EWP/560/95/Rev. 1 Corr. 2**
Committee for Human Medicinal Products (CHMP)

Guideline on the investigation of drug interactions

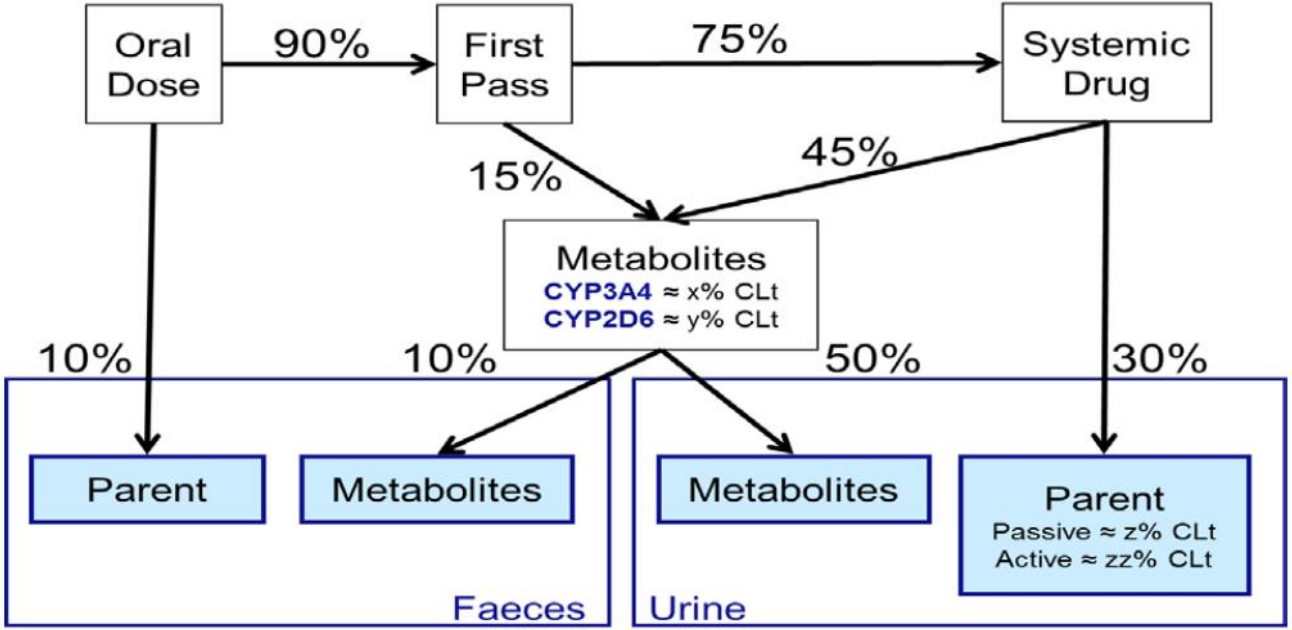
Enzyme and transporter based interaction



Victim – how is the drug eliminated??

- Guideline focuses on the importance of charaterising and quantifying the elimination pathways of the drug
- Importance of **mass-balance study**
- In vivo verification of elimination pathways contributing to >25% of the elimination
  Metabolism pathway normally verified in vivo with strong enzyme inhibitor
- If >25% eliminated through active secretion (renal, biliary/intestinal secretion) main responsible transporter (s) should be identified.
- If hepatic elimination >25% Study OATPs

Proposed illustration of a drug´s elimination



Perpetrator: Which substances should be screened?

- **Parent drug**

- **"Major metabolites“ (for CYPs only)**

- Phase I metabolites with an AUC that is both:
  - larger than 25% of the AUC of parent drug and
  - >10% of the total drug-related exposure (radioactive moieties in the human mass balance study)

Perpetrator: Enzyme inhibition in vitro
- guideline demands

Always

Both competitive and mechanism base inhibition should be investigated for:

CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A

"Optional"

- UGTs inhibition if one of the major elimination pathways of the investigational drug is direct glucuronidation.
- Inhibition of other enzymes being one of the major elimination pathways of the investigational drug

Should preferentially be conducted before phase III!

Perpetrator: Transporter inhibition in vitro
- guideline demands

Always

Transporters known to be involved in clinically relevant in vivo drug interactions

- **Uptake:** OATP1B1, OATP1B3, OCT2, OAT1, OAT3
- **Efflux:** P-gp, BCRP

- **"Optional"**

Transporters with indications of clinical relevance

- **Uptake:** OCT1
- **Efflux:** MATE1, MATE2, BSEP

- **Should preferentially be conducted before phase III!**

Concentration cut-offs to interpret in vitro data

- Intestine (Pgp, BCRP, CYP3A4, (UGT))

$$0.1 \times \frac{\text{Maximum single dose}}{250\ \text{ml}}$$

Intestinal volume content

- Systemic interactions **50x$C_{max,u}$** (liver enzymes, liver efflux transporters, renal transporters, liver uptake transporter after iv/sc/im administration)
- Hepatic inlet cutoff (liver uptake transporters for oral drugs)

$$25 \times (f_{u,b} \times (I_{max,b} + (F_a \times F_g \times k_a \times \text{Dose}/Q_H))$$

Perpetrator - induction

- CYP3A4 model for PXR induction
- CYP2B6 model for CAR induction
- CYP1A2 model for Ah receptor mediated induction

- Normally investigated in hepatocytes from 3 donors and evaluated in each donor separately, mRNA measured

- Positive signal – concentration dependent increase in mRNA, at least 2-fold increase at clinically relevant concentration

We recommend to summarise data in tables for submission

Cut-offs for the evaluation of interaction potential for direct comparison with Ki

	$50\times Cmax_u$[a] (µM)	25×Inlet Cmax(u)[a] (µM)	0.1×dose/250 ml[b] (µM)
Parent drug			
Metabolite 1		NA	NA
Metabolite 2		NA	NA

[a] Multiple dose Cmax, xxx mg dose (Reference)

[b] Based on a xxx mg dose (Reference). When relevant, provide information on solubility in biorelevant media (FaSSIF or FeSSIF depending on food intake recommendations).

NA - Not applicable

In vitro enzyme inhibition:

		Competitive inhibition	TDI	Positive or negative?
Enzyme	Substrate	Ki*# (µM)	KI (µM) # and Kinact (min-1)	
CYP1A2				
CYP2B6				
CYP2C8				
CYP2C9				
CYP2C19				
CYP2D6				
CYP3A4				
Optional enzymes…				

*include ">[highest studied conc. in µM] where relevant.

#based on unbound, actual concentrations available for interaction in the assay

Transporter	Substrate	In vitro system (Abbreviated)	Ki* # (µM)	IC50*# (µM)	Positive or negative?
P-gp					
BCRP					
OATP1B1					
OATP1B3					
OAT1					
OAT3					
OCT2					
MATE1					
MATE2					
Optional transporters					
BSEP					
OCT1					

* Fill in either Ki or IC50. Include ">[highest studied conc. in µM] where relevant.

#based on unbound, actual concentrations available for interaction in the assay

How to interpret in vitro data

- Normally **yes/no** answer, can a clinical interaction be excluded or not
- Basic model, compare the Ki to relevant guideline cut-off (reversible inhibition, induction)

- If positive basic model, there are more complex models that can be used to evaluate the in vitro result
  - Mechanistic static (for direct inhibition and/or TDI or induction; static concentration)
  - RIS for induction (Relative Induction Score) comparison to known inducers)
  - PBPK models (dynamic models, need qualification)

- If clinical interaction cannot be excluded this has to be studied in vivo in a DDI study and/or handled in the SmPC

- For reversible inhibition - negative in vivo data can be extrapolated to enzymes with higher Ki/IC50
- For induction – consider co-regulated enzymes and transporters

Other issues covered in EMA DDI-guideline, examples:

- Guidance on how to perform and present the mass-balance study
- Guidance on interactions at the absorption site e g pH dependent solubility, complex binding
- Guidance on food-effect studies
- Brief information about pharmacodynamic interactions
- Brief information about protein binding/displacement interactions

Issues discussed in published QA

www.ema.europa.eu

- *Alternative to 72 h incubation in in vitro induction studies?*

Shorter durations can be used if sensitivity is shown with known inducers

- *Background to cut-off*
- *CITCO recommended as positive control for CAR-induction*
- *Extrapolation of induction results on CYP3A4, 2B6 and 1A2 to other enzymes*
- *Duration of in vivo induction study*

10-14 days recommended to quantify CYP3A4 induction (if no accumulation)

Concept paper on GL update

Review

A summary of the current drug interaction guidance from the European Medicines Agency and considerations of future updates

Susan Cole [a,*], Essam Kerwash [a], Anita Andersson [b,c]

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[b] European Medicines Agency, Amsterdam, the Netherlands
[c] Medical Products Agency, Uppsala, Sweden

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New recommendations on:

- Inhibition and induction of enzymes in the intestine: specifying cutoffs for poorly soluble drugs. ICHM12
- Specific in vitro study design recommendations for in vitro induction studies: number of concentrations to study. 5 concentrations suggested
- Transport as rate limit for elimination: in vivo study design considerations.
- The addition of a table to present in vitro drug-drug interaction (DDI) information. Previous slide
- Specifying a cutoff (two-fold) for the inhibition constant 'Ki' shift to conclude mechanism based inhibition, including details regarding the pre-incubation duration. ICHM12
- In vitro induction screening: update on study design recommendations.
- Transporter inhibition screening: update of the list of transporters to screen from a pharmacokinetic perspective. ICHM12
- Transporter inhibition screening: update of some cutoffs for determining in vivo relevance of in vitro inhibition. ICHM12

Concept paper on GL update, cont´d

Clarifications on:

In vitro studies:

- The need to know whether the (unbound) target concentration was maintained in an in vitro system during the incubations.
- The use of Bile Salt Export Pump (BSEP) inhibition data.
- How to calculate the unbound inlet concentration.
- How to verify adequate sensitivity of the system for in vitro induction studies.

In vivo studies and labelling:

- How to present the mass balance study results: adding a recommendation on how to illustrate the elimination of a drug schematically.
- Discussing the text on interaction studies with oral contraceptives for potential teratogens.
- Specification of the presently recommended duration of in vivo studies of CYP3A4 induction[1].

Stability testing in experiment or from other data. Calculation of Ki based on actual concentration.

Risk for hepatotoxicity, not PK interaction

As shown on previous slide

Recommendation on safe methods (adding barrier method) if DDI data on OC is lacking

ICH M12, future for the EMA guideline

- ICHM12 will harmonise e g requirements regarding in vitro and in vivo studies on enzymes and transporters

- Some issues not covered by ICH M12 (such as absorption interaction, food interactions) will still be covered by EMA guideline

EMA PBPK guideline focuses on how to qualify and report models for DDI prediction

- To describe the expected content of PBPK modelling and simulation reports included in regulatory submissions
- Describes the documentation needed to support the qualification of a PBPK platform for an intended use
- Applies both to commercially available platforms and to in-house built platforms

13 December 2018
EMA/CHMP/458101/2016
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation

Draft agreed by Modelling and Simulation Working Group	April 2016
Draft agreed by Pharmacokinetics Working Party	May 2016

Table of Content

Understand how changes in key input parameters affect the model output

To certify that a PBPK platform can be used for an intended regulatory purpose

To certify that the drug model is capable of predicting the observed PK of the compound before the model can be used for simulations of special situations

Credibility Matrix, an assessor´s view of submitted PBPK models

- Question of interest
- Regulatory impact
- Platform qualification
- Precision level (sensitivity analysis)
- Risk based analysis of decision consequence
- Model informed decision

Concluding remarks

- EMA Guideline on the investigation of drug-drug interactions covers both enzyme/transporter interactions and other issues like food and absorption interactions
- Some updates have been planned but are awaiting the ICH M12 work
- Some adjustment of e g cut-offs and requirements regarding enzymes and transporters are likely after the ICH harmonisation work.
- PBPK guideline is focused on reporting and qualification of DDI models
- Assessment of PBPK in applications is made case-by-case and knowledge about the usefulness of PBPK in regulatory applications is evolving

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