50+ locations

Global availability of research models
and CRO services

5 continents

Extensive reach across the Americas, Europe, Asia, and the Middle East

3,800+ employees

Serving over 65 countries

150 years

Combined industry experience

$500 million

Approximately $500m in annual revenue

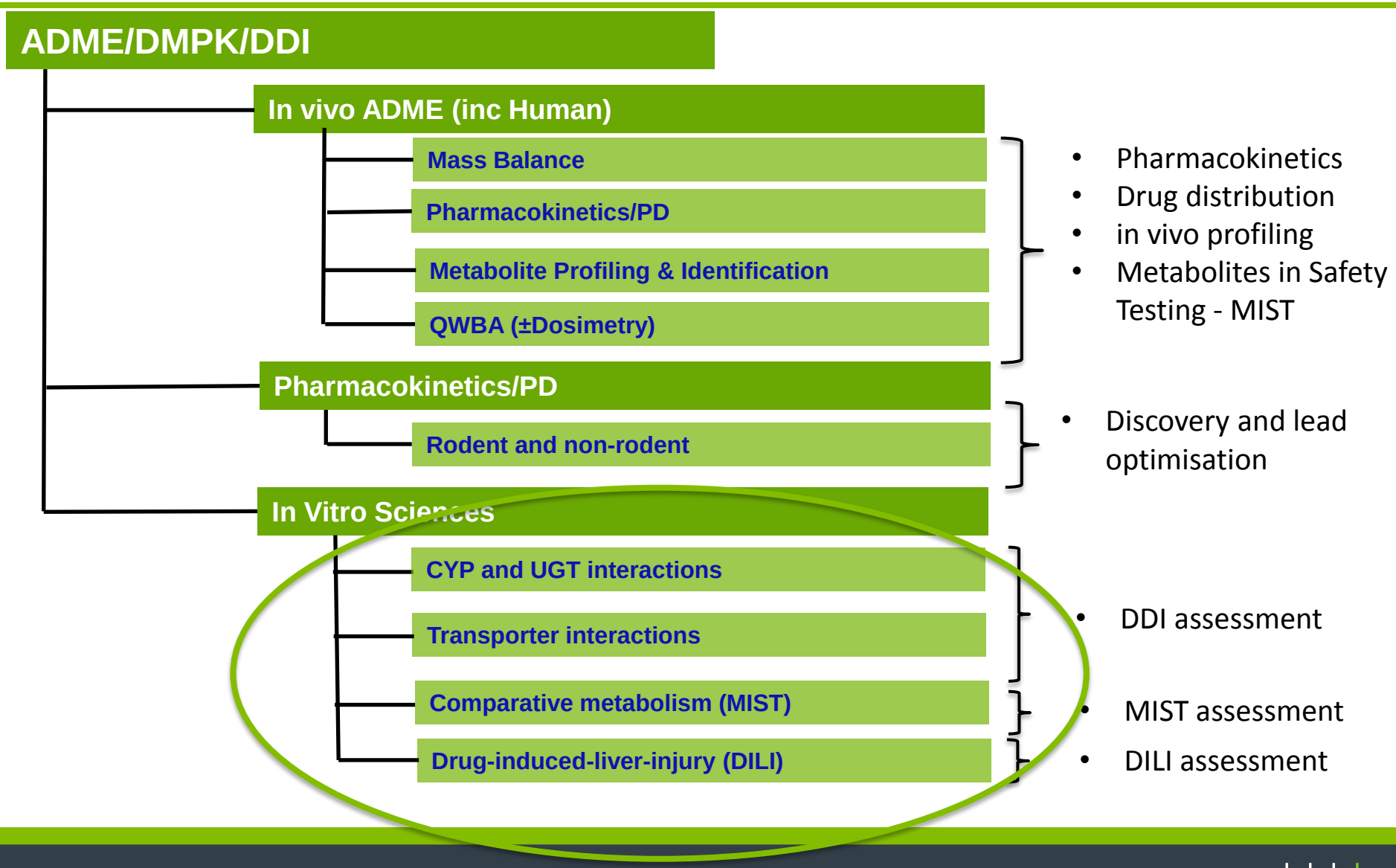
Guy Webber – based at Huntingdon CRS UK

Huntingdon
Cambridgeshire
UK

- Approx. 900 employees on site
- Providing global contract research services to:
  - Pharma - pharmacology, safety assessment (toxicology), DMPK, ADME, DDI
  - Non-pharma (environmental, chemical, veterinary) development services

ENVIGO

DMPK Service Areas at Huntingdon

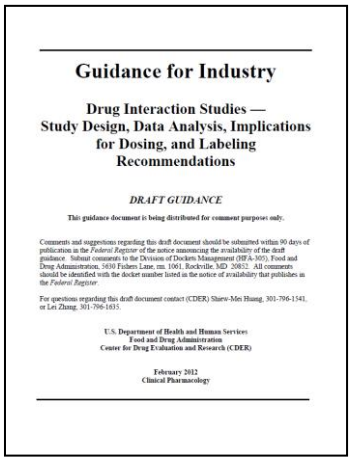


ENVIGO

DDI Assessment

Why? Patient safety

Driven by regulatory guidances:



Guidance for Industry

Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations

DRAFT GUIDANCE

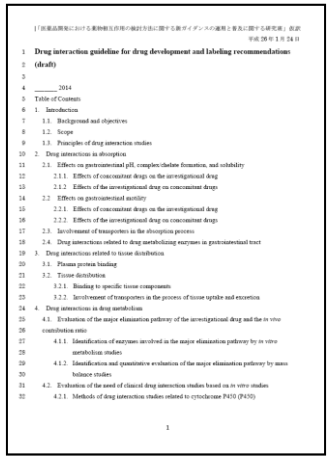
This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Shiew-Mei Huang, 301-796-1541, or Lei Zhang, 301-796-1635.

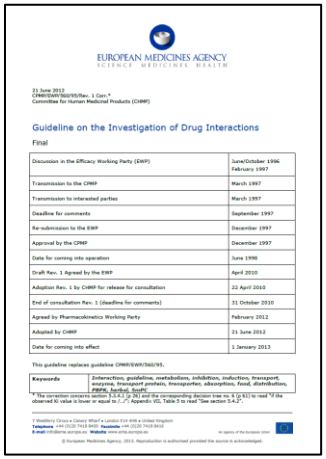
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

February 2012
Clinical Pharmacology



1 **Drug interaction guideline for drug development and labeling recommendations**
2 **(draft)**
3
4 _____ 2014
5 Table of Contents
6 1. Introduction
7 1.1. Background and objectives
8 1.2. Scope
9 1.3. Principles of drug interaction studies
10 2. Drug interactions in absorption
11 2.1. Effects on gastrointestinal pH, complex/chelate formation, and solubility
12 2.1.1. Effects of concomitant drugs on the investigational drug
13 2.1.2. Effects of the investigational drug on concomitant drugs
14 2.2. Effects on gastrointestinal motility
15 2.2.1. Effects of concomitant drugs on the investigational drug
16 2.2.2. Effects of the investigational drug on concomitant drugs
17 2.3. Involvement of transporters in the absorption process
18 2.4. Drug interactions related to drug metabolizing enzymes in gastrointestinal tract
19 3. Drug interactions related to tissue distribution
20 3.1. Plasma protein binding
21 3.2. Tissue distribution
22 3.2.1. Binding to specific tissue components
23 3.2.2. Involvement of transporters in the process of tissue uptake and excretion
24 4. Drug interactions in drug metabolism
25 4.1. Evaluation of the major elimination pathway of the investigational drug and the *in vivo*
26 contribution ratio
27 4.1.1. Identification of enzymes involved in the major elimination pathway by *in vitro*
28 metabolism studies
29 4.1.2. Identification and quantitative evaluation of the major elimination pathway by mass
30 balance studies
31 4.2. Evaluation of the need of clinical drug interaction studies based on *in vitro* studies
32 4.2.1. Methods of drug interaction studies related to cytochrome P450 (P450)

1



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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

Guideline on the Investigation of Drug Interactions

Final

Discussion in the Efficacy Working Party (EWP)	June/October 1996 February 1997
Transmission to the CPMP	March 1997
Transmission to interested parties	March 1997
Deadline for comments	September 1997
Re-submission to the EWP	December 1997
Approval by the CPMP	December 1997
Date for coming into operation	June 1998
Draft Rev. 1 Agreed by the EWP	April 2010
Adoption Rev. 1 by CHMP for release for consultation	22 April 2010
End of consultation Rev. 1 (deadline for comments)	31 October 2010
Agreed by Pharmacokinetics Working Party	February 2012
Adopted by CHMP	21 June 2012
Date for coming into effect	1 January 2013

This guideline replaces guideline CPMP/EWP/560/95.

Keywords	Interaction, guideline, metabolism, inhibition, induction, transport, enzyme, transport protein, transporter, absorption, food, distribution, PBPK, herbal, SmPC

* The correction concerns section 4.2.4.1 (p 26) and the corresponding decision tree no. 6 (p 41) to read "if the observed Ki value is lower or equal to [...]" Appendix VII, Table 5 to read "See section 5.4.2".

7 Westferry Circus ▪ Canary Wharf ▪ London E14 4HB ▪ United Kingdom
Telephone +44 (0)20 7418 8400 Facsimile +44 (0)20 7418 8416
E-mail info@ema.europa.eu Website www.ema.europa.eu An agency of the European Union

© European Medicines Agency, 2013. Reproduction is authorised provided the source is acknowledged.

(sometimes to increase efficacy)

ENVIGO

But in the real world of Dug Development…

RISK

The odds of developing a new marketed drug are 5/10,000 : 1
Average cost is now running at $1.4 billion (?)

Some major risks to drug development and drivers

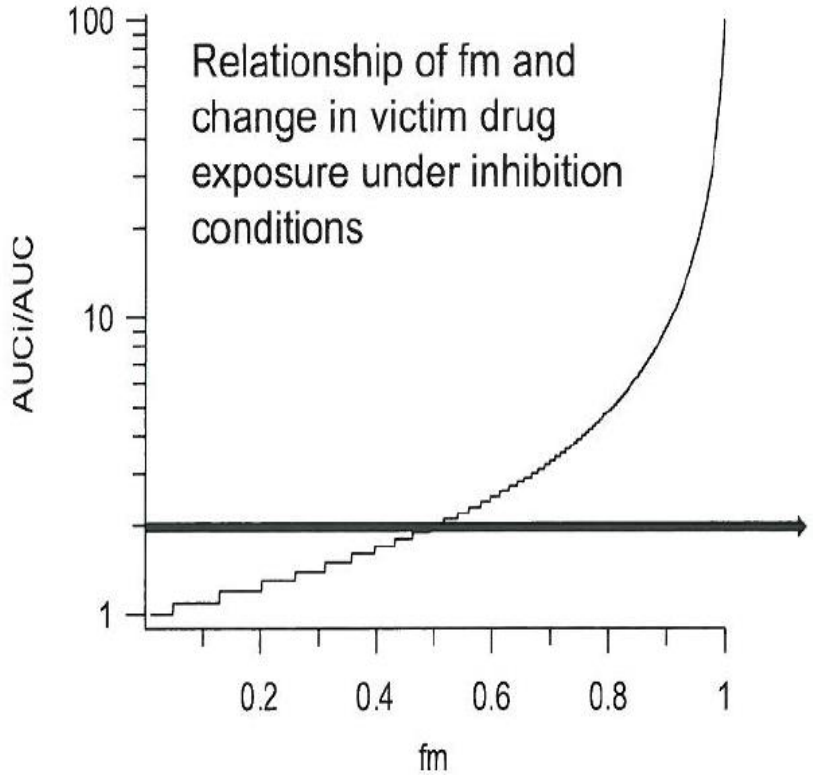
Phase of development	Major risk	Risk driver
During development	Non approval restrictive labelling PMC	**High DDI potential (VICTIM DRUG)**
NDA	Delay	**MIST issues - human specific metabolite(s)**
After development	Withdrawal from market	**Positive for DILI**

Risks are high as a victim drug

- If a drug is primarily cleared by a single enzyme or transporter ($F_m/F_t = 1$) and has a relatively narrow therapeutic range…it is at risk of:
  - Non approval (eg. debrisoquine, perhexilline)
  - Excessive labelling (competitor weakness)
  - Withdrawal (eg. terfenadine, cerivastatin, astemizole, cisapride)
- *In vitro* reaction phenotyping studies can efficiently tell you about F_m and F_t and help define your risk as a victim drug early!
  - Clearance mechanism:
    - Lipophilic, neutral - metabolism
    - Charged - transport

Why is victim drug status so important?

Rationale for FDA victim drug risk assessment and recommendation for rigorous phenotyping (substrate) studies - DDIs (change in AUC of victim drug) can be greatly magnified if a single enzyme or transporter dominates the clearance of a drug, that is, if F_m or F_t = approaches 1 :



Fm <0.5 MAY not be clinically relevant depending on safety, but any pathway contributing ≥25% will require identification

Reaction Phenotyping

IMO - Reaction Phenotyping studies are one of the most important studies in all drug development – provides the information:

i) which enzymes and transporters are involved in the clearance of your drug, defining DDI risks
ii) PK variation (polymorphic expression of DMEs and TPs)

(FDA now recommend prior to Phase I)

(Do it right…do it radiolabelled ☺)

Department of Metabolism at Envigo

- Specialists in DMPK and In Vitro Sciences
  - Radiochemistry
  - Discovery & Regulatory ADME programmes
  - In Vitro and DDI Sciences
  - Metabolite profiling and Metabolite ID
  - QWBA
  - Human mass balance studies
- 60 Scientists
- GLP, GCP, GMP, FDA inspected

- Provide decision making data for Regulatory submissions and

and clinical support but also developing early risk assessment strategies to help highlight if a molecule carries a potential metabolic liability (so that major investment decisions can be more judiciously made)

DDI

VALUE INCREASING

DDI assessment program	Drug 1	Drug 2
Testing drug as perpetrator of DDIs		
CYP inhibition	✓	✓
CYP induction	✓	⚑
UGT inhibition	✓	✓
Efflux transporter(s) inhibition	⚑	⚑
Uptake transporter(s) inhibition	✓	✓
Testing drug as victim of DDIs		
CYP phenotyping (substrate interactions)	✓	✓
UGT phenotyping (substrate interactions)	✓	⚑
Efflux phenotyping (substrate interactions)	✓	⚑
Uptake phenotyping (substrate interactions)	✓	✓