Safeguarding public health

Can PK and Modelling Help?

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for an ageing population
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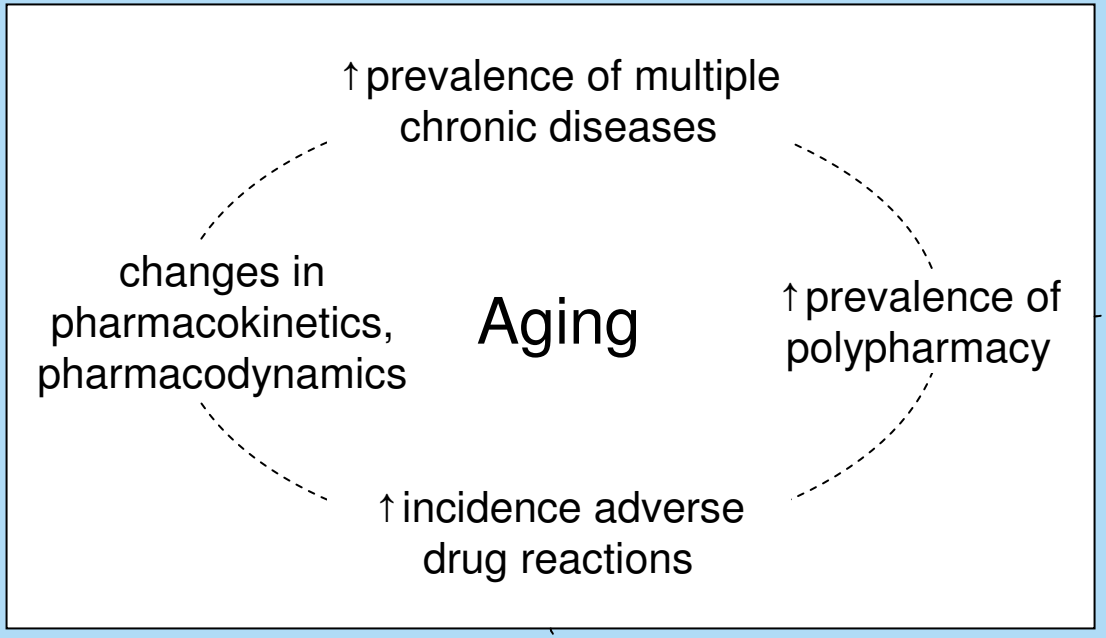
Disclaimer

The views expressed in this presentation are those of the speaker, and are not necessarily those of MHRA or EMA

Problem Statement



Management of drug therapy

"start low · go slow"

"hit hard · start high · go fast"
(antimicrobials, anticancer)

Older adults underrepresented in clinical trials
(relative to disease prevalence)

Benefit/risk

Generalizability?

(Posology with age and polypharmacy?)

EMA Vision for a geriatric strategy: TWO PRINCIPLES

Medicines used by geriatric patients must be of high quality, and appropriately researched and evaluated.. **for use in this population**.

→ Evidence based medicine

PK and Modelling

Improve the availability of **information** on the use of medicines for older people

→ Informed prescription

Key questions: Are we collecting the "right" information?
Can we do more with what we have?

Age related changes in PK

Changes of the physiological functions in elderly subjects and their impact on pharmacokinetics	
Physiological changes	**Possible pharmacokinetic effect**
Absorption	
↑ gastric pH	↑ gastric pH ↓ absorption of **pH-dependent drugs**
	↑ absorption of **acid-labile drugs**
↓ small intestine surface and blood flow	↓ absorption
↓ gastric emptying and bowel motility	↓ or delayed absorption
Distribution	
↑ adipose tissue, ↓ muscle mass	↑ t1/2 of **lipophilic drugs**
↓ body fluid	↑ concentration of **hydrophilic drugs**
↓ plasma albumin	↑ free concentration of **acidic drugs**
↑ plasma α1-acidic glycoprotein	↓ free concentration of **basic drugs**
Metabolism	
↓ hepatic blood flow	↓ first-pass metabolism
Elimination	
↓ renal blood flow, ↓ rate of glomerular filt	↑ half-life of **renally eliminated** substances

Depends on physicochemical properties of drug elimination mechanisms

≈ predictable

Adapted from Bellmann-Weiler, Gerontology 2009; 55:241-249.

Age related changes in renal excretion

life-long oxidative stress → **compromised tubular function**

Manifestations
- telomere shortening
- ↓ expression of the klotho antiaging gene
- tubular atrophy
- ↓ organic acid, proton, potassium clearance
- ↑sclerotic, ↓functioning glomeruli
- ↓GFR (0.75 ml/min per year after age 40)

- ↓ CYP450 activity, metabolic clearance
- ↓plasma, tissue binding

Not homogenous (1/3 have no change with age)

Serum creatinine = **poor indicator**

Age related changes in PD

Enhanced CNS effects
- benzodiazepines
- anaesthetics
- opioids
- antipsychotics

- altered neurotransmitters and/or receptor conc
- hormonal changes (sex, growth hormones)
- ↓ glucose, oxygen (↓cerebrovascular function)
- **↓ Pgp function**

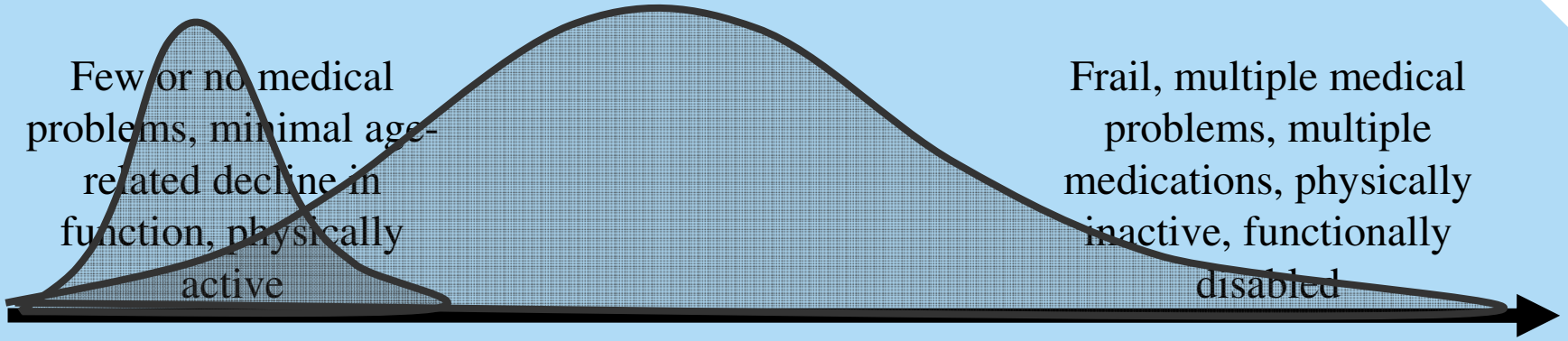
Enhanced cardiovascular drug effects
- calcium channel blockers
- ß-adrenergic agents
- diuretics
- warfarin

NSAIDS

Impact of age on PD less predictable than impact on PK

Corsonello, et al. *Current Medicinal Chemistry*, **17:**571-584 (2010).

Elderly are the most heterogeneous age group



Prescription = same as younger population

How to inform prescription?

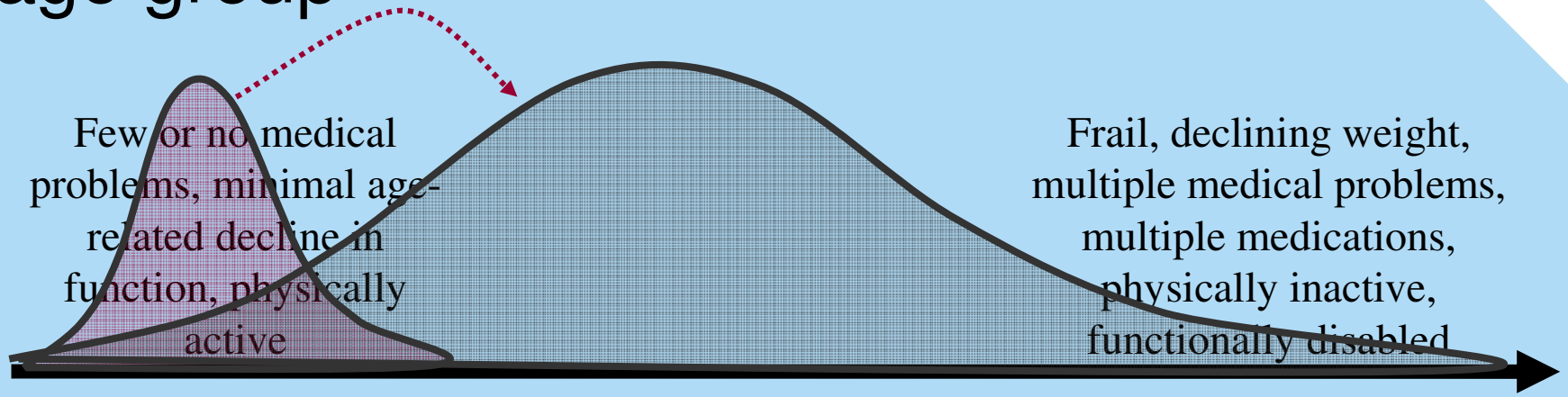
Demographics of clinical trial population = patient population?

if YES

Need **informative** covariates

- Chronological ≠ "physiological age"
- Frailty
- Normal aging versus co-morbidity
- Renal function ≠ serum creatinine

Elderly are the most heterogeneous age group



Prescription = same as younger population

How to inform prescription?

if NO

Recognise extent and impact of **extrapolation**.

Elderly take more drugs

Elderly = **13%** of US population, receive **34%** of all prescriptions, consume **40%** of non-prescription medications.
Qato, et al. *JAMA.* **300**:2867–2878 (2008)

Highest medication prevalence in women > 65 years;
23% use ≥ **5** medications; **12%** use ≥ **10** medications.
Rosenthal, et al. *Blood Press*. **17:**186-94 (2008)

Higher incidence in hospital and nursing home settings
Schmader, et al. *Mayo Clin Proc.* **85:**S26-S32 (2010)

Challenge for **informed prescription**
- ↑ probability DDI
- different DDI risk to young, healthy
- too many combinations to test

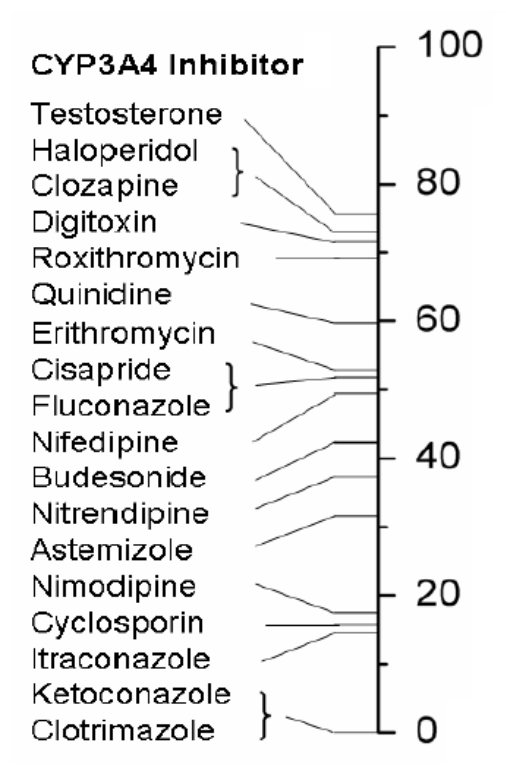
Risk of DDIs depends on drug elimination mechanisms: **Example**

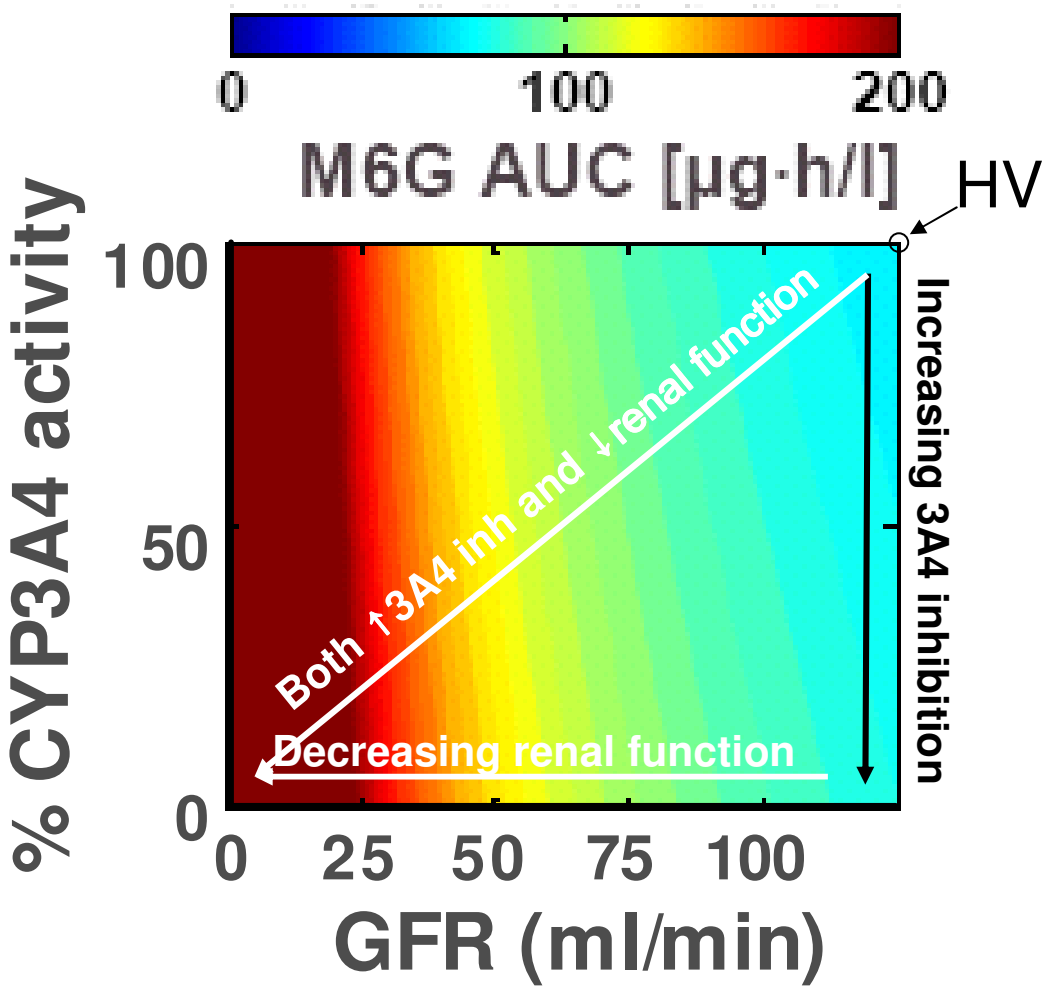
- Codeine is a widely used analgetic and anti-tussive drug
- Codeine is metabolized by two polymorphic enzymes, CYP2D6 and UGT2B7 and CYP3A4 (minor)
- **CYP2D6 and UGT2B7 metabolites (morphine and morphine-6-glucuronide, M6G) can lead to respiratory depression**
- Codeine, morphine and M6G renally eliminated

Risks assessed:

- What, if a CYP3A4 inhibitor is co-administered?
- What, if kidney function is impaired?
- What, if a combination of both occurs?

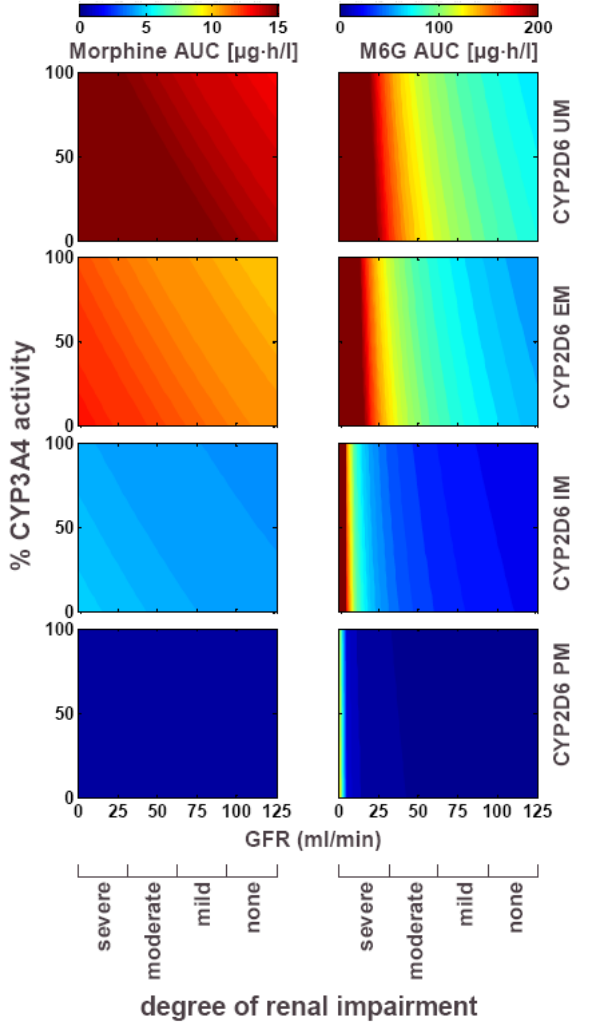
Risk of DDIs … example (cont'd)





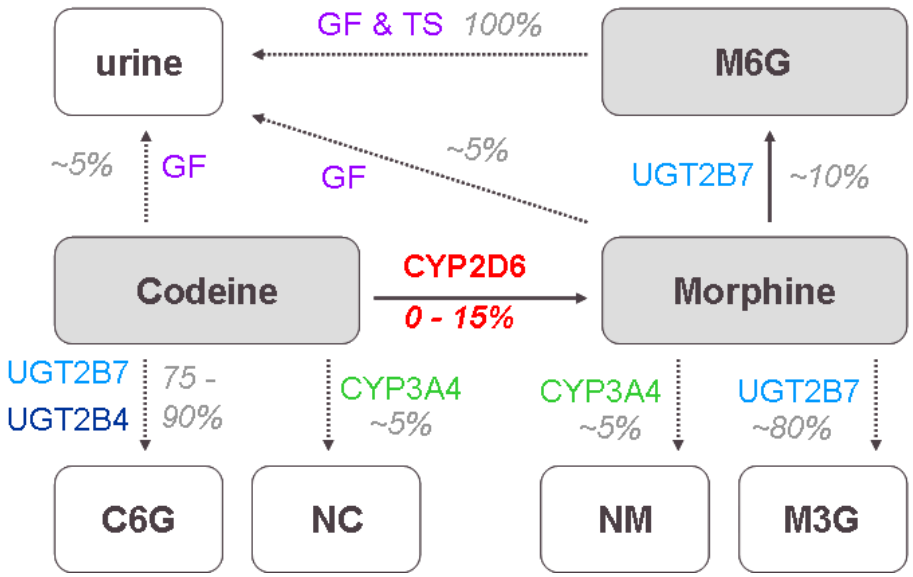
Risk of DDIs … example (cont'd)

- What, if a CYP3A4 inhibitor is co-administered? — ***rather safe !***
- What, if kidney function is impaired? — ***rather safe except in ESRF***
- What, if a combination of both occurs? — ***potentially dangerous for CYP2D6 UM & EM with moderate RI***



Tools for DDI risk assessment

Codeine **mass balance**:



\+ **PBPK model** with blood flows, tissues volumes, etc.

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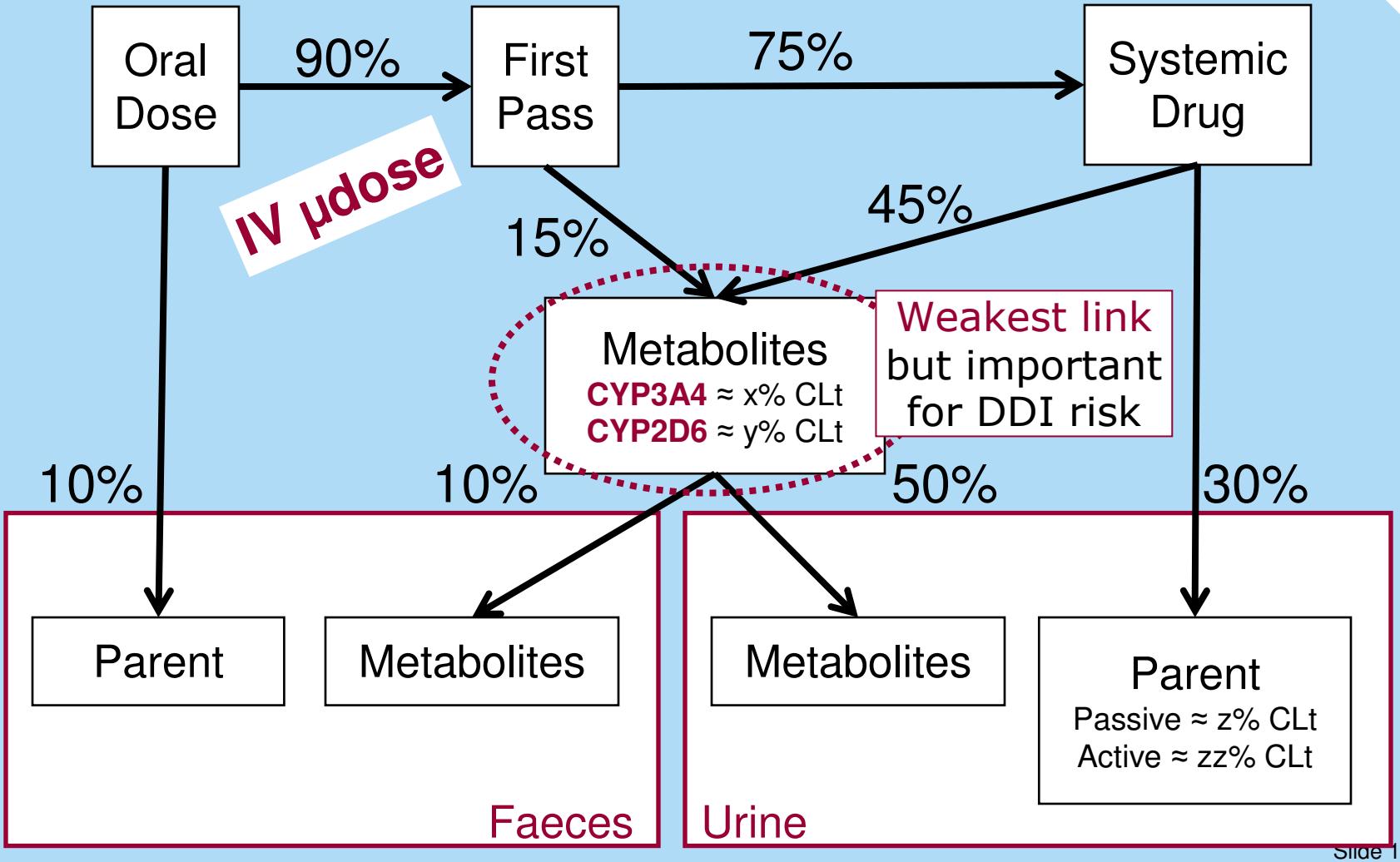
\+ Drug clearance, binding, etc

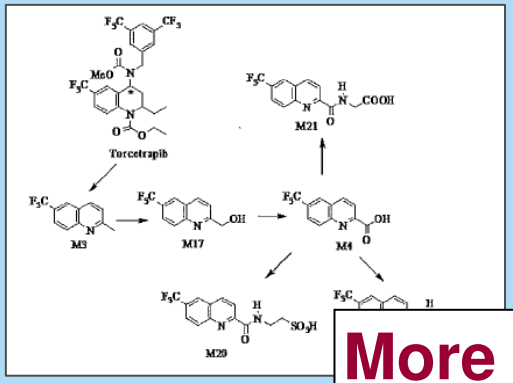
Mass balance example from dossier for NCE



Typical information in dossier: **optimal** for DDI risk assessment?

In vitro metabolism studies
- Human microsomes, hepatocytes
- Purified enzymes
- Addition of specific inhibitors

In vivo studies
- Excretion balance study (radioactivity in excreta, metabolic profiling)
- Correlation of in vivo metabolites to in vitro pathways
- Co-administration of enzyme inhibitors
- Studies in extensive and poor metabolisers



More useful if integrated across studies

Quantitative integr
- Scaling
- ivo data (with and without inhibitors, extensive metabolisers, etc)

if can't predict → understand drug elimination mechanisms ? → ↓ confidence for extrapolation

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Summary: How to inform prescription?

Key questions: Are we collecting the "right" information?
Can we do more with what we have?

Informative covariates
- "physiological age", co-morbidity, frailty
- renal function measure appropriate for elderly (≠ SCr)

Recognise and evaluate impact of **extrapolation**
- critical to understand routes, mechanisms of elimination
- be quantitative and mechanistic (software available)
- overcome pre-clinical/clinical PK model divide
- PK currently more predictable than PD

PK and Modelling

Continue to **learn** about the impact of aging
(PKPD, systems biology, …)

Informed prescription