CBG MEB

# Guideline on the use of Pharmacogenetic Methodologies in the Pharmacokinetic Evaluation of Medicinal Products

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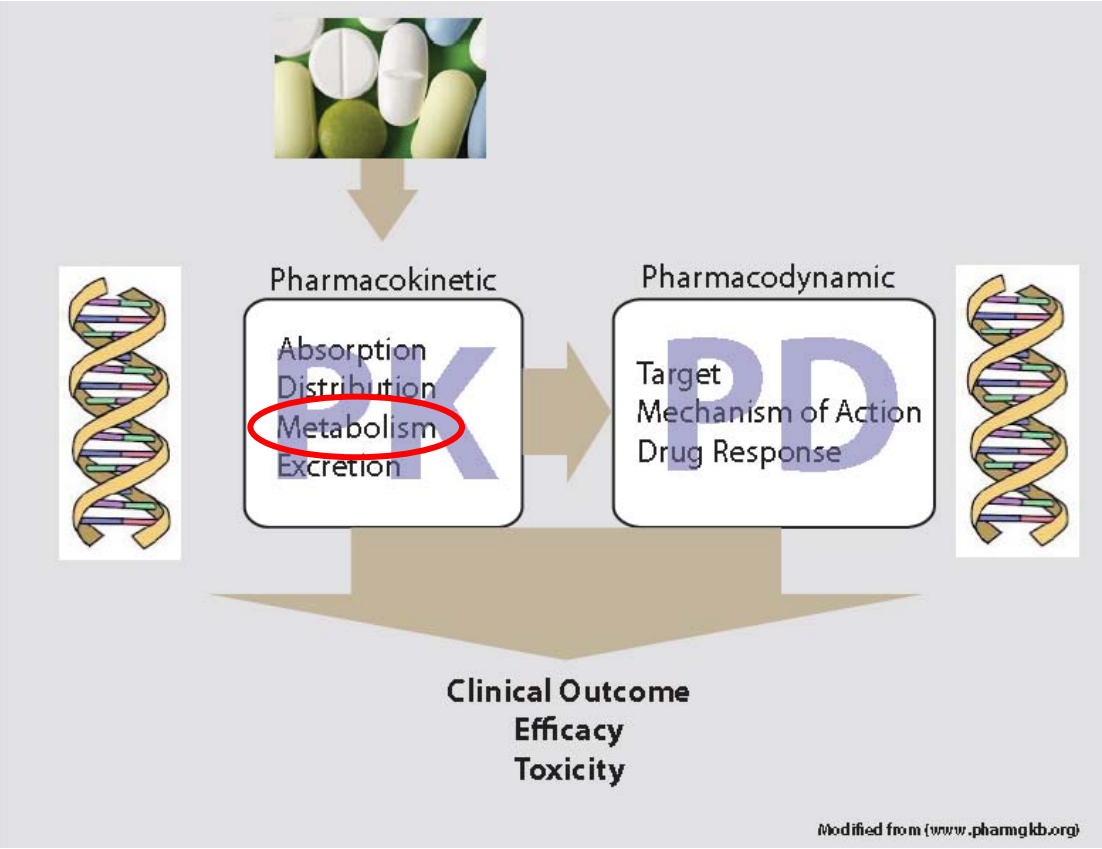
# Interindividual differences in drug response



## **Metabolism** and transport

- Metabolizing enzymes account for ~80% of those that are mentioned for PGx purposes on current drug labels.

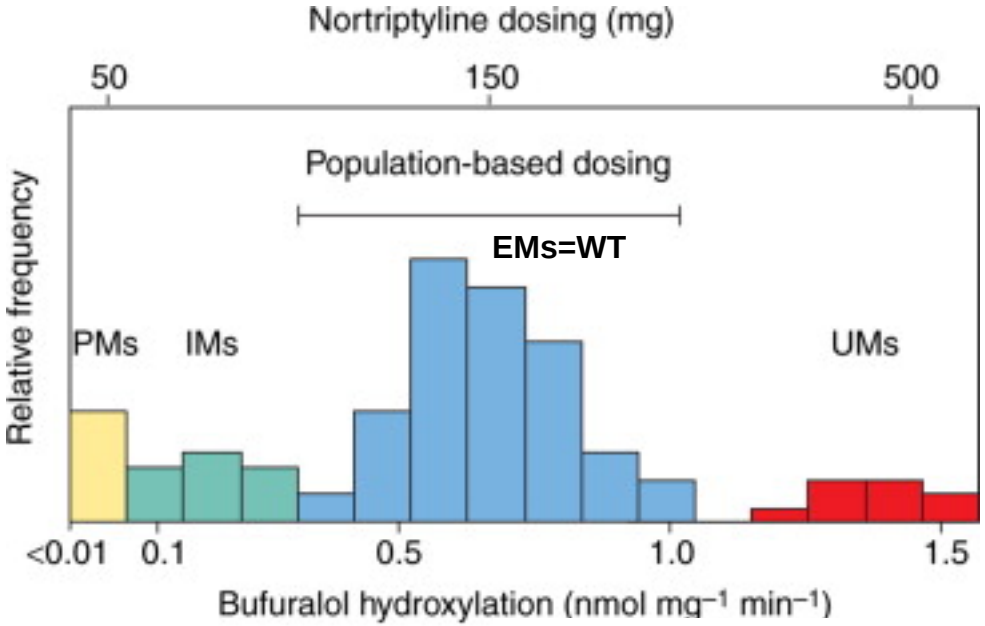
- Genomic variations in phase I or phase II metabolizing enzymes may lead to

  (i) **increased or decreased clearance** of the **parent drug** and/or its pharmacologically active or toxic metabolites,

  (ii) **increased or decreased production** of **active metabolites** from the respective prodrugs, or

  (iii) **increased or decreased formation** of **toxic metabolites**.

# Metabolising capacity




**CYP2D6 homozygous deletion**

**CYP2D6 heterozygous deletion**

**CYP2D6 two normal alleles**

**CYP2D6 duplicated multiplied**

Figure from: Ingelman-Sundberg, Trends in Pharmacological Sciences, 2004

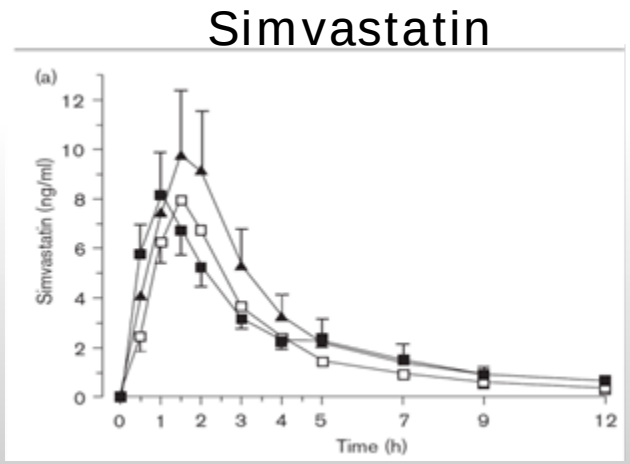
# Metabolising capacity, examples

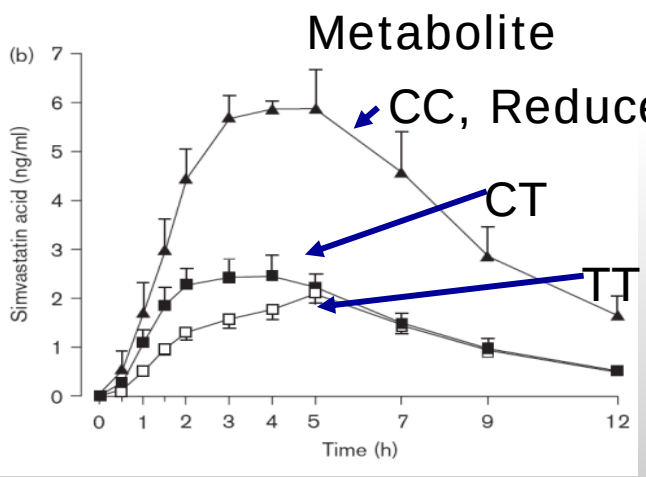
- Antidepressants, antipsychotics (2D6) and anticoagulants (2C19). Exposure varies dependent on genotype.
- Codeine, tramadol (2D6), clopidogrel (2C19). Excessive prodrug activation in UMs
- Clopidogrel. Activation is diminished in CYP2C19 PMs.

- Pharmacogenetically-based **variations in PK may affect the clinical PD** of a drug and the associated benefit/risk considerations.

# Drug transporters

- Drug transporters **may affect ADME** as well
- Example: SLCO1B1 (organic anion transporter protein 1B1, OATP1B1) polymorphism: alters the PK and associated ADRs of drugs like statins




Passanen et al., Pharmacogen Genom 16:873-879 (2006)

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# Guideline on the use of pharmacogenetic methodologies in the pharmacokinetic evaluation of medicinal products


# Guideline

- **Situations and stage**(s) where PGx-related PK studies should be performed.
- **Regulatory considerations** and/or requirements for PGx-related PK studies (e.g. study design, selection of subjects, and sampling) .
- Information on **evaluation of clinical impact of PG findings**, and type of supporting studies for posology and treatment recommendations.
- **Treatment recommendations** and labeling.
- Special considerations on integration of drug-drug interactions (**DDIs**), and **impaired or immature organ function** in conjunction with PGx-related PK issues.


# Requirements and recommendations…

- Further investigations into PG related to PK are **required** when:

a) in vitro and/or clinical studies indicate that a **known functionally polymorphic enzyme or transporter** is likely to be *important* in the disposition of the drug, or

b) in vitro and/or clinical studies indicate that a **known functionally polymorphic enzyme or transporter** is likely to be *important* in the formation, elimination or distribution of a **pharmacologically active or toxic metabolite**, or

c) clinical studies indicate that **substantial interindividual differences in the PK of the drug** which can not be explained by other intrinsic or extrinsic factors are likely to influence the efficacy or safety of the drug in a genetically variable subpopulation.


# Requirements and recommendations…

- Further investigations into PG related to PK are **recommended** when:

a) available *in vitro* data indicate that a **polymorphic enzyme or drug transporter contributes to the PK** of the active substance, but that the quantitative role is relatively low based on the *in vitro* data, *or*

b) there is high interindividual **PK variability**, or there are **PK outliers** with higher or lower exposure to the active substance that cannot be attributed to other known intrinsic or extrinsic factors, but which could *possibly* give rise to clinical efficacy and/or safety concerns based on the existing knowledge, *or*

c) **major PK differences** are observed between **ethnic groups** that cannot be attributed to other known intrinsic or extrinsic factors


# Important…

- Not always clear in early phase if genetic variation is important for efficacy and safety
- Cut-off values to base decision on:
- Important: **in vitro** data predict **>50%** is cleared by a **single functionally polymorphic enzyme**
- Important: **>25% of parent** drug cleared by the polymorphic enzyme **in vivo**

- Arbitrary, but though over…


# When to do what?

*In vitro* **Studies prior to human Exposure**

In Vitro Metabolism Studies
(human enzymes)

A single functionally polymorphic enzyme
≥ 50% of metabolism

YES

NO

Phase I

First in Man:

Genotype all Individuals included in the Study

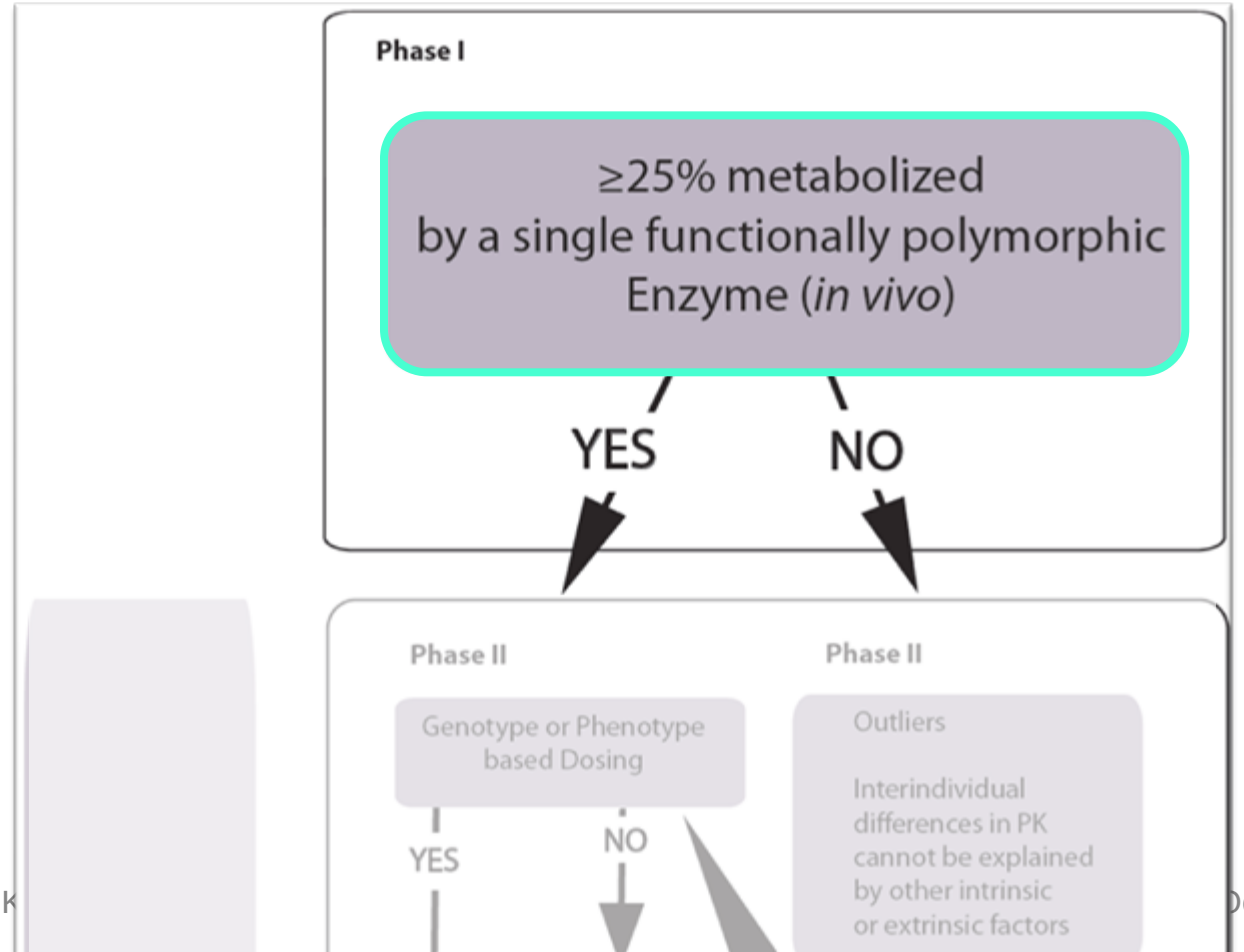
adjust starting Dosage

Phase I

Outliers

Interindividual differences in PK cannot be explained by other intrinsic


# When to do what?




# Triggers for the need of PGx guided studies…

- …at later developmental stages

a) a **previously unknown or sparsely studied** functionally polymorphic enzyme or drug transporter is found to be involved in the metabolism or transport of the medicinal product that is being developed, *or*

b) the enzyme or drug transporter involved in the metabolism or transport is known but there is **no prior knowledge regarding functional polymorphisms** of the gene, *or*

**c) PK outliers** are observed throughout phase I to phase IV studies.


# DNA banking

- In all clinical phases of drug development, **prospective banking of DNA** for genotype analysis is **highly recommended**.

- Ensures/increases chance that unknown genomic variations can be identified and their clinical effects tested with adequate power.


# Retrospective analysis

- Conclusions from **retrospective analyses** carried out in response to emerging data may be acceptable for genetic issues related to PK if :
  - they are **mechanistically supported** by available in vitro or PK information.
  - DNA from a **representative proportion of patients** enrolled in the phase I, II and III studies is available.

- If **new PK genetic associations** are discovered:
  -complementary *in vitro* or PK examinations aimed at investigating the mechanism of action and **confirming** the PK consequences are expected.


# Meta-analysis

- meta-analyses on pooled data from different PK or clinical studies can be considered.
- **Standardization of studies** with respect to non-genetic factors (e.g. in- and exclusion criteria, sampling schedule) throughout the clinical development is advised.
- In this way meta-analyses on pooled data is facilitated, which may be used to increase predictive performance.


# Clinical consequences/treatment recommendations

- **Clinical consequences** of genomic variations depend on:

a) magnitude of drug exposure caused by the polymorphism,
b) relationship between PK and PD of the medicinal product,
c) relationship between drug dose and clinical effect/ADRs *and*
d) severity of possible ADRs and/or clinical consequences of reduced efficacy.


# Clinical consequences/treatment recommendations

- **Treatment recommendations**:
- **Principle:** unless it is reliably shown that a difference in active substance and metabolite exposure has little consequence on efficacy and safety, the EMA expects **genomic variations related to PK to be compensated with dose adjustments.**
- Either genotype or phenotype based dosing *or* individual dose titration based on Therapeutic Drug Monitoring (TDM).
- If dose titration based on clinical markers is applied, data ensuring satisfactory efficacy and/or safety within the genetically defined subpopulation must be provided.

# Conclusions

- Pharmacogenetics should be an integral part in drug development, starting early.
- Aim should be to obtain a clear dosing or treatment recommendation, yielding effective and safe treatment, also in the genetic subpopulations.


# Backup slides


# Clinical consequences/treatment recommendations

- **Design of Phase III studies**. Possibilities envisioned:

  a) previous data: difference in exposure **may** lack clinical relevance.

- Aim: **dosing irrespective of genotype/phenotype**
- Goal of the phase III study: to confirm presumed lack of clinical significance.
- Claim must be supported by conclusive clinical data obtained from those exposure levels.
- Enrichment for genetically defined patients in phase III (Low prevalence: additional EM treatment arm implementing larger doses may be needed).


# Clinical consequences/treatment recommendations

b) previous data: difference in exposure **likely** of clinical relevance.

- Aim: **genotype/phenotype based dosing**
- Genotype/phenotype based dosing regimen yielding comparable dosages was developed in phase I and phase II studies.
- Posology of active substances in phase III to be adjusted on a genotype/phenotype basis
- Sparse sampling with population-PK analyses in phase III studies to confirm the dose normalization.


# Clinical consequences/treatment recommendations

c) previous data: difference in exposure **likely** of clinical relevance.

- Aim: **Dose titration regardless of genotype** (if suitable markers exist).
- The phase III study should aim to confirm that there are no efficacy and/or safety concerns for the genetically defined subpopulation when the proposed general dose titration is applied.
- PK and PD data related to efficacy and safety may be supportive in this respect.


# Physiologically based PK (PBPK)

- In case of well validated in silico Physiologically Based Pharmacokinetic (PBPK) models for polymorphic enzyme systems:
- PGx differences in humans may be predicted and used as a **guide for clinical study design** with respect to PGx investigation