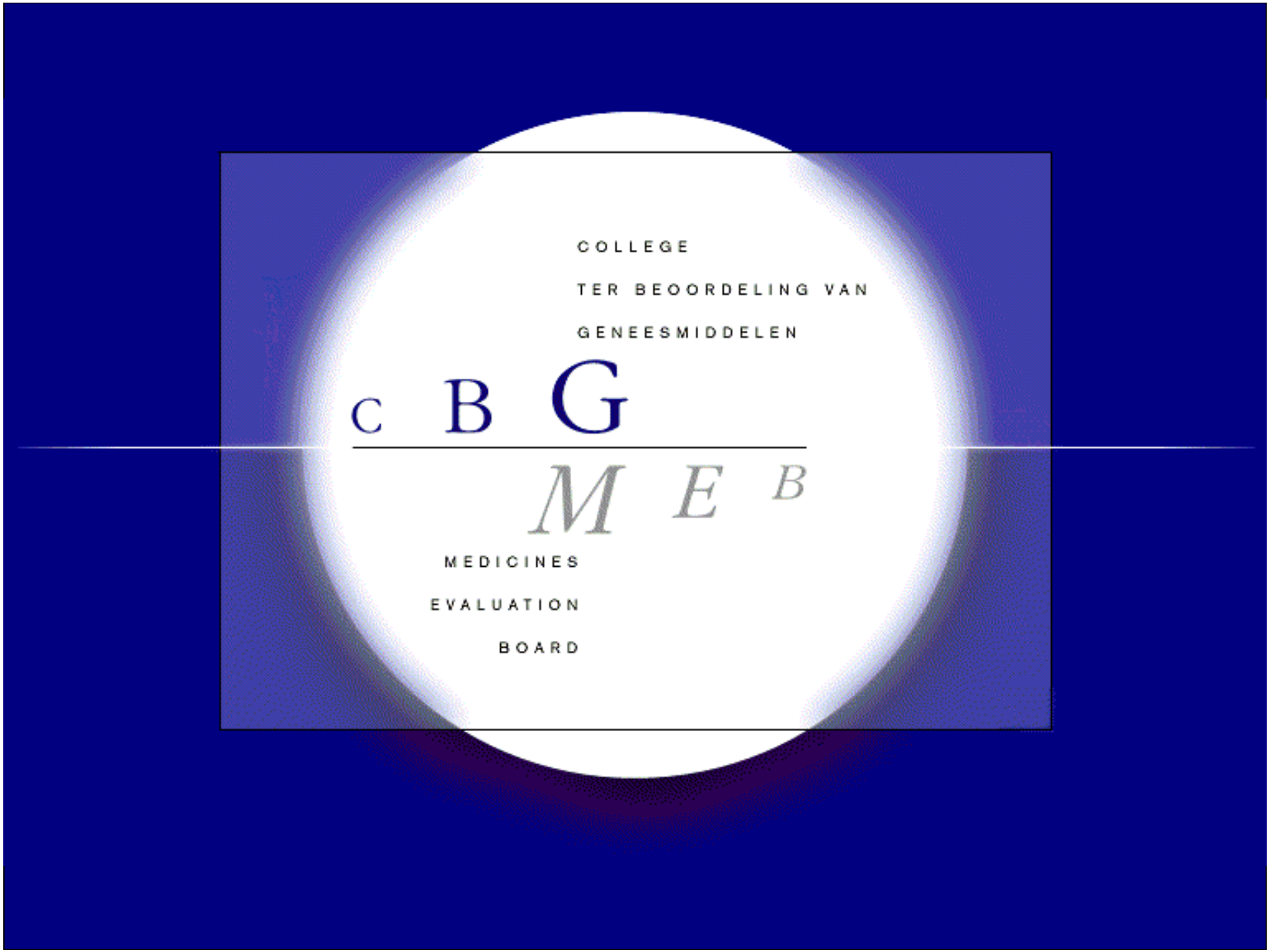
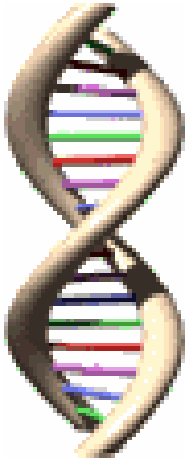

COLLEGE
TER BEOORDELING VAN
GENEESMIDDELEN
CBG
MEB
MEDICINES
EVALUATION
BOARD

Applications of PGx in PK at EMEA: experience and expectations



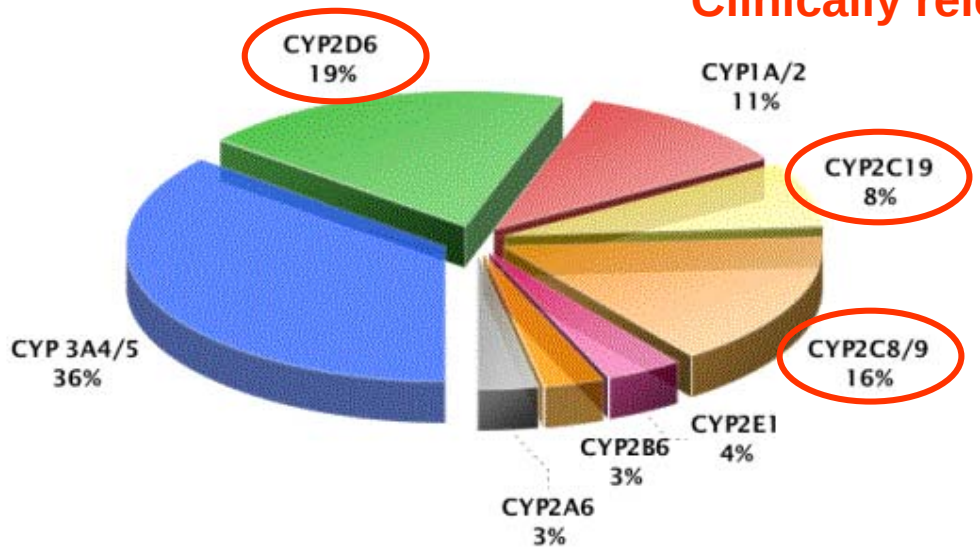
Marc Maliepaard

PGWP

- History
- Current reflection paper on PG in PK studies
- New proposed Guideline on PG in PK studies

History

Proportion of Drugs Metabolized by P450 Enzymes



Clinically relevant polymorphism

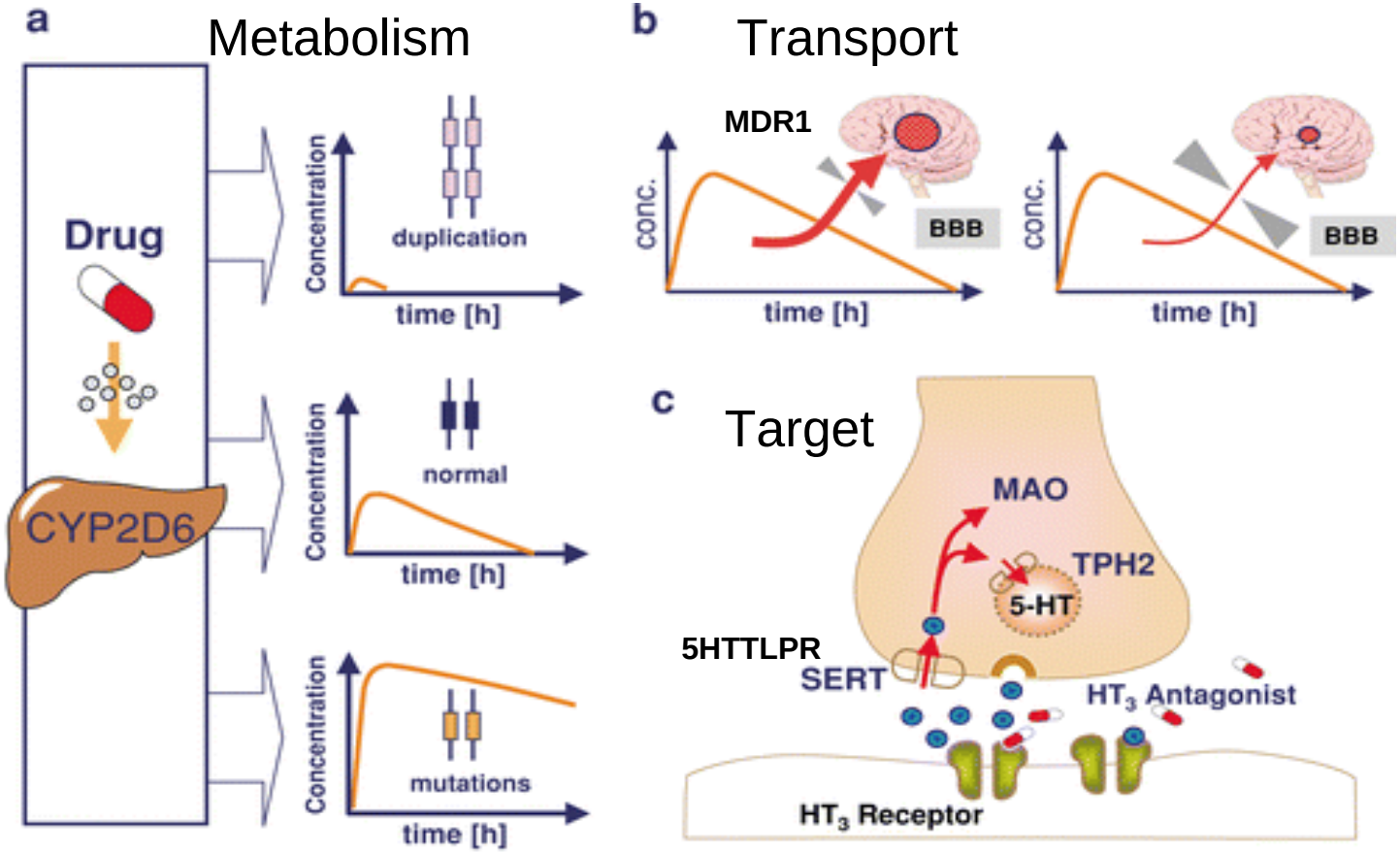
Adapted from: Wrighton SA et al. Crit Review Toxicology 1992;22:1-22.
Kashuba and Bertino. Mechanisms of drug interaction. In Drug Interactions in Infections Diseases. Humana Press. 2001.

History

- Not only CYPs:
- UGTs
- N-acetyltransferase 2
- Methyltransferases

- Others…

Polygenic influence on drug action



Eichelbaum, Ingelman-Sundberg, Evans: *Annu Rev Med* 57 119-37, 2006

History

- Regulatory experience:

  -Requirements PGx in PK studies only briefly described (e.g. in human PK guideline, paediatrics)

- Dossiers:
- Often metabolism studied late =>

  -active metabolite not captured

  -influence of PG also known late!

- Studies, reports different quality/depth

Reflection paper PGx in PK evaluation

- General aims:
- Harmonize development and reporting of PG/PK studies
- Inform on possible consequences of PGx data for label

Reflection paper PGx in PK evaluation

European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

London, 25 May 2007
EMEA/128517/2006

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

REFLECTION PAPER ON THE USE OF PHARMACOGENETICS IN THE PHARMACOKINETIC EVALUATION OF MEDICINAL PRODUCTS

- Started drafting in 2006, adopted by the CHMP in May 2007

Reflection paper PGx in PK evaluation

- Scope:

-When should effect of PG on PK be studied?

-At what stage in the clinical development program?

-Study design and methodology

-Evaluation of the clinical consequences of PG-PK differences

-Drug-drug interactions and impaired/immature organ functions

-Treatment recommendations based on important PG related differences in exposure

3. When should effect of PG on PK be studied?

- When polymorphism occurs, but:
- Only when this polymorphism translates into important differences in systemic or local exposure.
- Effect on active substance and/or active/toxic metabolite
- PG-related effects can affect Absorption, Distribution, Metabolism, and Excretion

3. When should effect of PG on PK be studied?

- PG studies are NOT necessary when:
- The polymorphism is not functional nor related to altered enzyme/transporter function or PK
- Functionally polymorphic enzyme is not the primary metabolism enzyme for a drug
- If polymorphism is extremely rare

3. When should effect of PG on PK be studied?

- Transporters: in vitro systems are less established
- Store samples for retrospective analysis if important interindividual variation in PK occurs with unknown genetic origin
- If in vitro data indicate transporters to be involved: in vivo studies are *encouraged*
- This was in 2006. At that time hardly examples known on clinical relevant transporter related polymorphisms.

3. When should effect of PG on PK be studied?

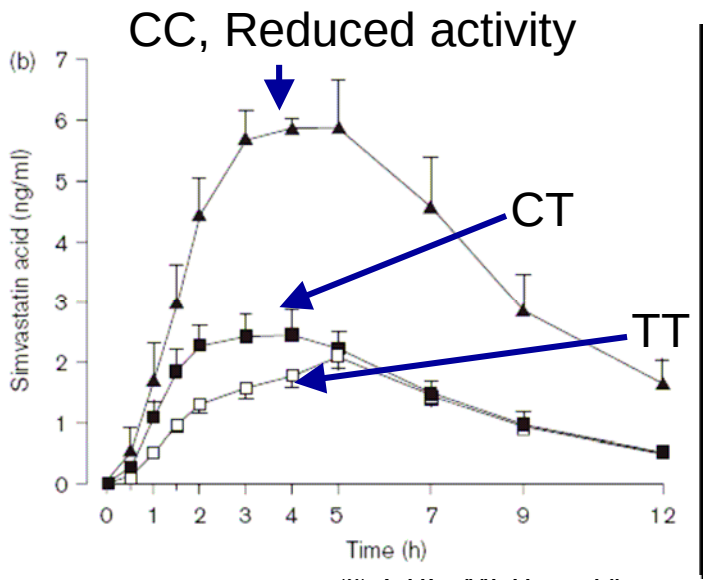
- But now in 2008 examples on statins, e.g.:

SLCO1B1 polymorphism markedly affects the pharmacokinetics of simvastatin acid

Marja K. Pasanen, Mikko Neuvonen, Pertti J. Neuvonen and Mikko Niemi

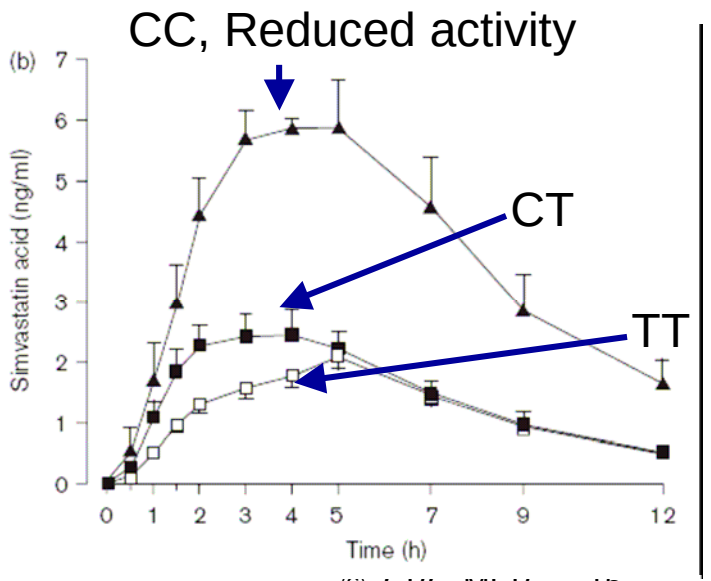
Pharmacogenetics and Genomics 2006, Vol 16 No 12

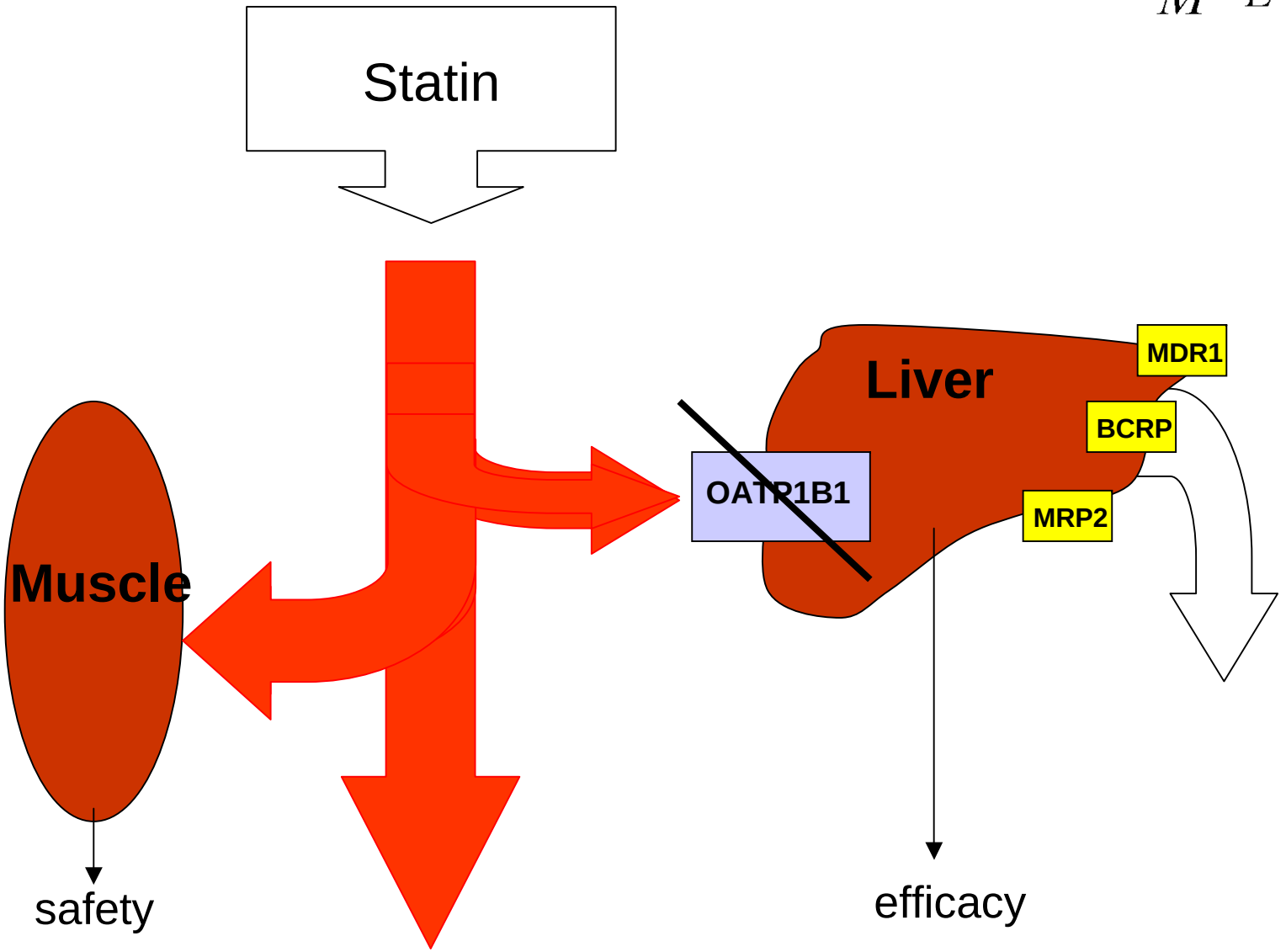
- SLCO1B1 encodes hepatic uptake transporter OATP1B1
- Polymorphism (Ala174Val) affects exposure to active simvastatin-acid metabolite

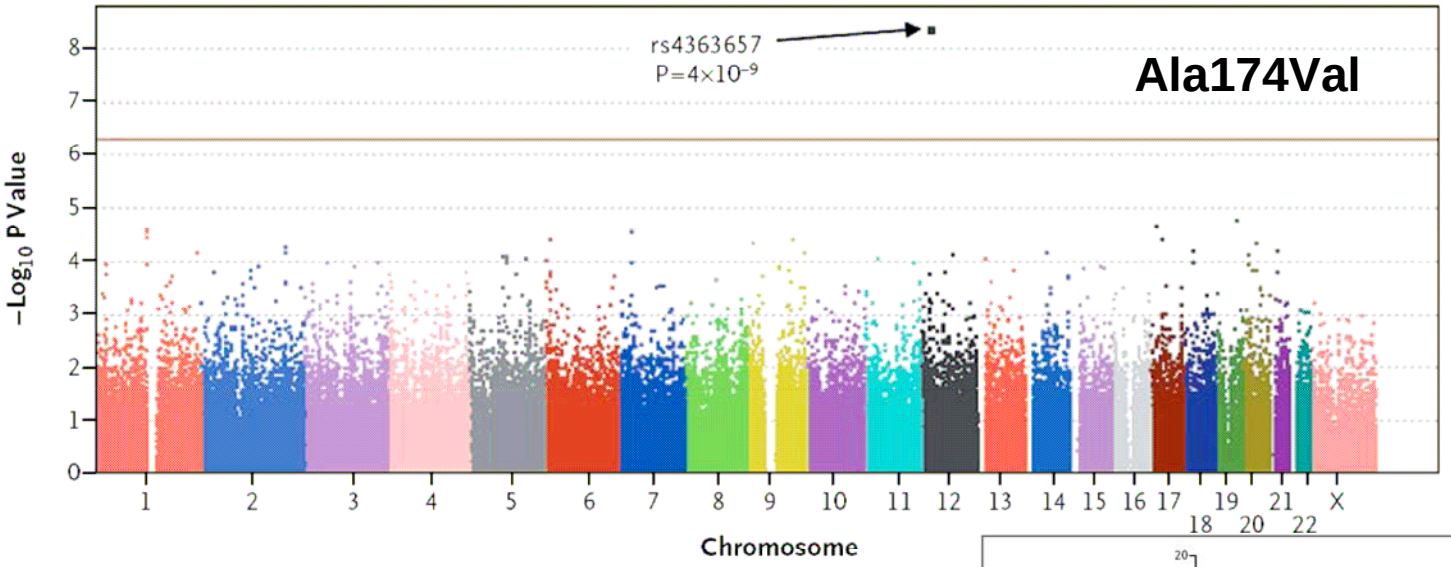


3. When should effect of PG on PK be studied?

- Possibly increased AE, and reduced efficacy
- Paradox: inactive OATP1B1 variant yields higher plasma levels, but reduced PD activity:
- Cause: Reduced uptake in the liver, site of action.




Statin
Liver
MDR1
BCRP
MRP2
OATP1B1
Muscle
safety
efficacy

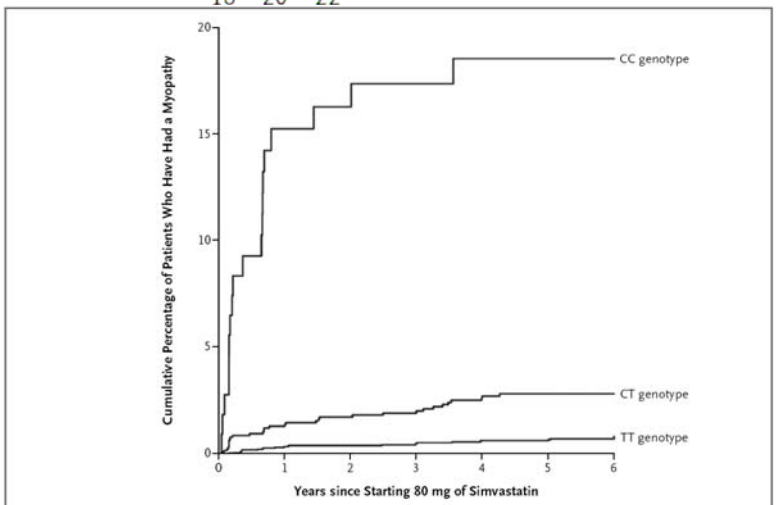


318 000 SNPs

SLCO1B1 Variants and Statin-Induced Myopathy — A Genomewide Study

NEJM 359 : 789, August 21, 2008

Estimated Cumulative Risk of Myopathy Associated with Taking 80 mg of Simvastatin Daily, According to *SLCO1B1* rs4149056 Genotype.



Cumulative No. and Percentages with Myopathy

Genotype	Population Frequency	Year 1				Year 5			
				Attributable to gentoype				Attributable to gentoype	
		no.	%	no.	% of total	no.	%	no.	% of total
TT	0.730	12	0.34	0	0	21	0.63	0	0
CT	0.249	17	1.38	12.8	75	32	2.83	24.9	78
CC	0.021	16	15.25	15.6	98	19	18.55	18.4	97
All genotypes	1.000	45	0.91	28.4	63	72	1.56	43.3	60

3. When should effect of PG on PK be studied?

- Transporter data may be complex, but effects may be clinically significant.
- Studies are ‘recommended’ instead of ‘encouraged’
- If indicated, target organ exposure could be studied

4. At what stage in clinical development should PG/PK studies be performed

- As early as possible
- When in vitro data show involvement of known polymorphic enzyme, preferably in Phase I.
- Genotyping towards candidate gene could be implemented in Phase I
- In general: when new polymorphism candidates are identified possibly explaining unexplained PK variability, incorporate this in subsequent clinical trials as soon as possible.

4. At what stage in clinical development should PG/PK studies be performed

- When genotype is known to be involved in PK:
- Genotyping is encouraged in as many Phase I, II and III trials as possible, in order to increase recommendations in genetic subpopulations.
- Dose-response studies or clinical studies in genetic subpopulations
- If not, suboptimal efficacy may be obtained, since
  -dose may be too low in Phase III, based on AE observed only in Poor Metabolisers
  -too low dose for Ultrarapid Metabolisers

5. Study design and methodology

- Either conventional PK of population PK approach
- Sufficient number of patients should be included
- Sometimes difficult with rare polymorphisms

- Genotyping methods:
- Not only SNPs, but also Copy Number Variation should be identified by the method.

6. Evaluation of clinical consequences of genetic differences on exposure

- Note: only relevant when relevant PG-related differences are present.
- Important parameters:
  -Magnitude of difference in exposure
  -Relationship between exposure and clinical effects/adverse events
  -Severity of adverse events and consequences of loss of efficacy.

6. Evaluation of clinical consequences of genetic differences on exposure

- Assessment based on clinical dose-ranging studies, PK/PD studies, clinical data in genetic subpopulation vs study population as a whole.

7. Drug-drug interactions and impaired or immature organ functions

- DDI: Consider parallel pathways if major metabolism pathway is absent
- Effect inhibition may be different in patients with absent or low activity
  (e.g., olsalazine, effect inhibition TPMT on toxicity thiopurine drugs is more pronounced in intermediate than extensive TPMT metabolisers)

7. Drug-drug interactions and impaired or immature organ functions

- Consequences of impaired organ function may be different in different PG subpopulations
- Also in elderly, possibly differences in metabolism, combined with reduced organ function => effect polymorphism may be different
- Ontogeny: qualitative and quantitative differences in enzymes/proteins, most marked in newborn, infants and toddlers (<2 years)

8. Treatment recommendations based on PG determined differences in exposure

- Three options

1. Dose titration regardless of genotype
   Titration schedule should be suitable for general population as well as PG subpopulation
2. Dosing based on genotype or phenotype
   If dose titration is not desirable or feasible, or safety and efficacy is a major concern
3. Optional gene based dosing
   If variability is undesirable (e.g., Quality of Life).

8. Treatment recommendations based on PG determined differences in exposure

- Other labelling consequences:
- Use 4.2 posology, 4.3 contra-indications, 4.4 warnings ‘as usual’
- Mention known (important) polymorphisms not investigated in detail for this drug (e.g. due to rare appearance)
- Indicate the difference in PK in subpopulations in 5.2
- Frequency of alleles of interest in different ethnic populations.

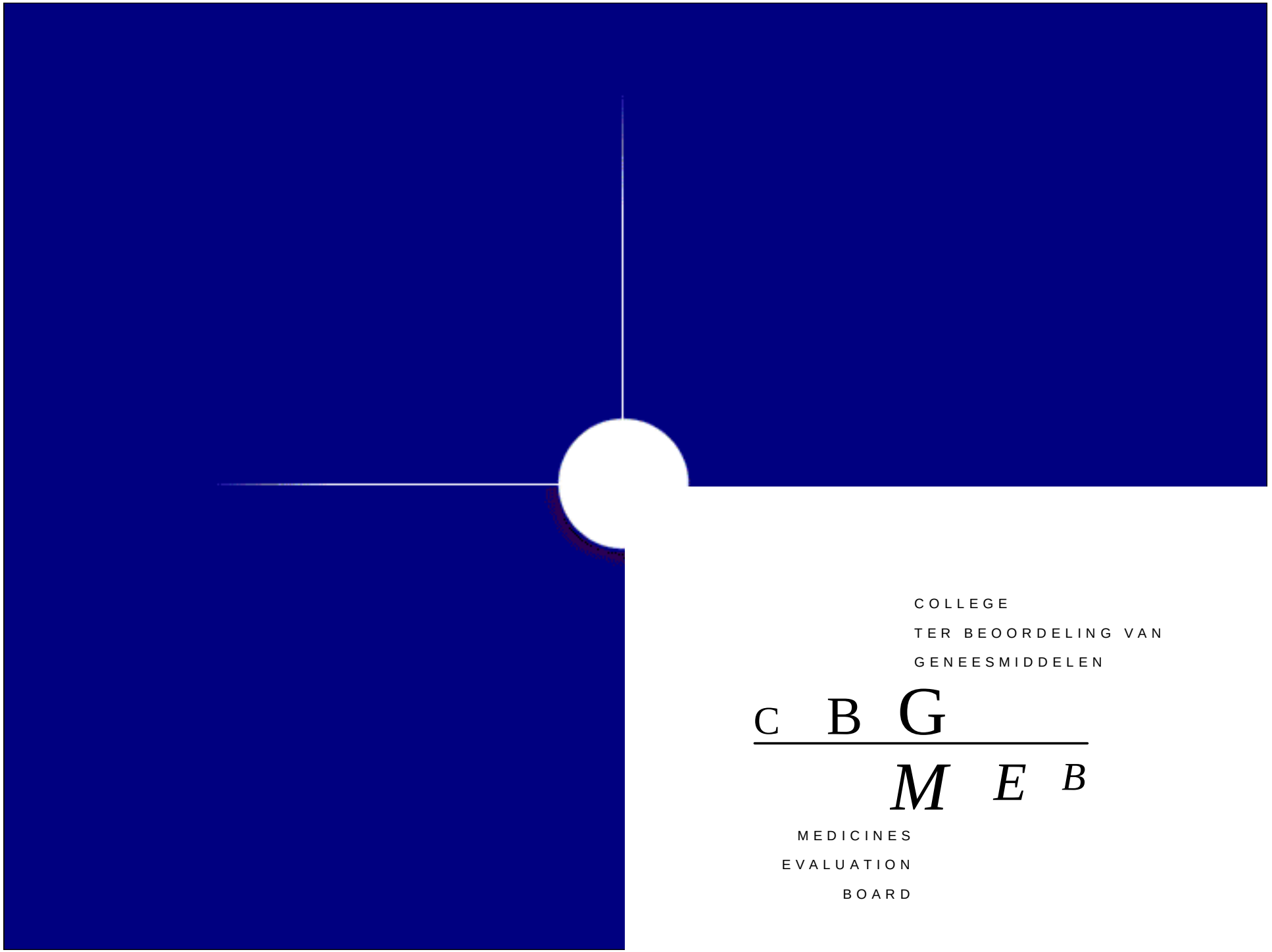
Guideline PGx in PK evaluation

- Is this reflection paper suitable to convert it into a Guideline?

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ~~REFLECTION PAPER~~ ON THE USE OF PHARMACOGENETICS IN THE ~~PHARMACOKINETIC EVALUATION OF MEDICINAL PRODUCTS~~ PHARMACOKINETIC EVALUATION OF MEDICINAL PRODUCTS

- Timeline: out for consultation Q3 2009
- Stakeholders: Points of agreement and disagreement
- Additional important issues to be covered in a Guideline?



COLLEGE
TER BEOORDELING VAN
GENEESMIDDELEN

CBG

MEB

MEDICINES
EVALUATION
BOARD