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

DRAFT RELEASED FOR CONSULTATION	July 2006
END OF CONSULTATION (DEADLINE FOR COMMENTS)	October 2006
AGREED BY PHARMACOGENETICS WORKING PARTY AND EFFICACY WORKING PARTY	April 2007
ADOPTION BY CHMP	May 2007

Comments should be provided electronically in word format to PGWPsecretariat@emea.europa.eu
For further information please visit our website http://www.emea.europa.eu/human/itf/itfguide.htm

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 13
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

1 BACKGROUND

In recent years a rapid development in our understanding of the genetics behind the interindividual differences in drug action has occurred. This encompasses the area of pharmacogenetics (PG) where the interindividual variability in genes related to drug transporters, drug metabolising enzymes and drug targets is studied in relation to efficacy of drug treatment and adverse drug reactions. A good deal of this variability may result from genetic polymorphism, i.e. the occurrence in the same population of multiple allelic states. With respect to pharmacokinetic (PK) aspects, the highest penetrance of genetic polymorphism is registered at the level of drug metabolism where about 40 % of phase I metabolism of clinically used drugs is affected by polymorphic enzymes. Well known polymorphic cytochrome P450 enzymes include CYP2D6, CYP2C19, and CYP2C9. Regarding phase II enzymes, the genetic variability of UDP-glucuronosyltransferases, N-acetyltransferase-2 and some methyltransferases are known to play a role in the interindividual variability in PK. The additional contribution of polymorphism in drug transporters has recently been recognised. In practice genetic variations are demonstrated by the identification of Single Nucleotide Polymorphisms (SNPs), insertions/deletions and variation in gene copy number (copy number variation, CNV).

This reflection paper intends to target the place of PG in the clinical PK evaluation of medicinal products during drug development and use. It should be read in connection with the following guidelines:

-Pharmacokinetic studies in man (Notice to applicants, Vol 3C, C3a, 1987)
-Guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population (EMEA/CHMP/EWP/147013/2004)
-The investigation of drug interactions (CPMP/EWP/560/95)
-Note for guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98)
- Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with impaired hepatic function (CPMP/EWP/2339/02)
-Note for guidance on the evaluation of the pharmacokinetics of medicinal products in patients with impaired renal function (CHMP/EWP/225/02)
-Position paper on terminology in Pharmacogenetics (EMEA/CPMP/3070/01)
-Reflection paper on pharmacogenomic samples and data handling (EMEA/CHMP/201914)
-A guideline on summary of product characteristics (EMEA/CHMP/64302/2005)
-ICH Topic E 15: Establish definitions for genomic biomarkers, pharmacogenomics, pharmacogenetics, genomic data and sample coding categories (CHMP/ICH/437986/2006)

2 SCOPE OF THIS PAPER

The following issues are discussed in the document:

-In which situations should the effect of PG on PK of new or existing medicinal products be studied
-At what stage in the clinical development program should PG/PK studies be performed
-Study design and methodology
-Evaluation of the clinical consequences of genetic differences in drug substance exposure
-Special considerations related to drug-drug interactions and impaired or immature organ functions
-Treatment recommendations based on genetically determined differences in exposure

The broader issue of pharmacogenomics (PGx), i.e. the variability in the entire genome relevant to drug response, will not be considered in this reflection paper.

3 IN WHICH SITUATIONS SHOULD THE EFFECT OF PG ON PK BE STUDIED

Studies of the effect of PG on PK are required for PK evaluation of a new chemical entity if the genetic variation is likely to translate into important differences in the systemic and/or local exposure to this substance or its active or toxic metabolites, thereby potentially affecting safety and efficacy of the treatment. PG variants may impact on Absorption, Distribution, Metabolism and Excretion of the compound.

Furthermore, combined PG/PK studies that may contribute to the identification of novel polymorphic loci are encouraged if the compound exhibits important inter-individual PK variability, likely to affect clinical efficacy and/or safety. Technology has advanced to the point that analysis of genetic factors affecting safety and efficacy of medicines is now fast and reliable. If there is clinically important variability in PK and genetic causes for this may not be excluded, it is advisable to carry out genetic analysis of loci likely to be responsible for this variation. In all cases where unexplained PK variation has been identified, samples for pharmacogenetic purpose should be collected. This would allow a critical evaluation of the clinical and, if population PK is used, PK consequences of this polymorphism at a later stage.

Studies of PG differences in the activity and expression of transport proteins involved in drug distribution (efflux or influx) to target organs such as the central nervous system, possibly explaining adverse events or lack of therapeutic effect, are encouraged if there are indications of clinically important differences in these respects and if a relevant polymorphism can be studied using cohorts with sufficient power to reach conclusions.

Although some polymorphisms are extremely rare, the applicant should always consider studying the PK and clinical consequences of all potentially clinically relevant polymorphisms. If this is not feasible, the applicant should justify the lack of data and discuss the possible safety (or efficacy) consequences based on prior knowledge on the effect of the polymorphisms on protein activity. Lack of data should be reflected in the Summary of Product Characteristics (SPC) if considered clinically relevant.

4 AT WHAT STAGE IN THE CLINICAL DEVELOPMENT PROGRAM SHOULD PG/PK STUDIES BE PERFORMED

In general, the importance of PG for the PK of a drug substance may be indicated by *in vitro* data where the enzymes involved in drug metabolism as well as formation and metabolism of pharmacologically active metabolites have been identified. Preclinical animal studies should be interpreted with great caution, as there are usually marked species differences. If human *in vitro* data suggest major involvement of a protein known to be subject to functionally important genetic polymorphism, inclusion of genotyping directed to the candidate gene is warranted in early phase I studies. When the involvement of the polymorphic gene has been verified, *in vivo* studies of the effects of specific polymorphisms on the PK of the pharmacologically active compounds likely to contribute to clinical efficacy and/or safety are recommended.

Involvement of transporters may also be indicated by *in vitro* data but presently the knowledge in this field is not mature enough for early genotyping to be required only on the basis of *in vitro* data. However, if the *in vitro* data together with other data such as ADME or renal excretion data indicate that a polymorphic transporter has a major role in the PK of a drug, genotyping in the subsequent PK studies and clinical studies is encouraged.

It is recommended that samples from the early phase I studies are stored to allow retrospective analysis, when more experience has been gained or new proteins have been shown to play a major role in the PK of the active substances.

In case of unforeseen PK observations of potential clinical relevance, such as marked interindividual variability or inexplicable outliers in phase I or subsequent studies, PG/PK studies should be performed as early as possible in the drug development program, once plausible candidate polymorphisms have been identified. Observation of clinical efficacy or safety problems suspected to be due to PK variability (see section above) may also trigger the need of appropriate PG/PK or other PG related studies at any stage of drug development.

When the genotype is predicted or known to markedly affect the PK of pharmacologically active compounds contributing to *in vivo* efficacy and/or safety of a medicinal product, genotyping is encouraged in as many of the phase I, II and III clinical studies as possible to increase the amount of data that will support the recommendations for use in the genetic subpopulation(s). Dose-response studies or other clinical studies covering the exposure of active substances obtained can be used to support safety and efficacy in a specific genetic subpopulation.

5 STUDY DESIGN AND METHODOLOGY

Conventional PK analysis and population PK analysis
The investigation of the effect of PG on the PK of a drug substance may be performed using a population PK approach in genotyped subjects and patients, or in a conventional PK study. In both cases the study should include a satisfactory number of patients of each geno- or phenotype in order to obtain valid correlation data. Power calculations should preferentially be done before the initiation of the study to ensure a sufficient study size. If a genotype is rare, phase I studies with selected inclusion of subjects of this genotype could be useful if feasible. It is acknowledged that stratification by genotype is difficult for very rare genetic variants but in many cases the effect of a particular rare genetic variant could be large and influences the specific treatment substantially. Pooled analysis of study data may be valuable in case selected inclusion is not possible due to very low allele frequencies. Investigations should focus on variations/alterations in genes causing anticipated functional effects on gene expression or function of the gene products, thus resulting in marked alterations in phenotype. If a need to base dosing on PG has been identified, it is likely that a specific PG/PK study is needed to support dose selection, unless sufficient data has been obtained in earlier studies.

Genotyping methods and choice of alleles
The genotyping methods should first be validated and then maintained under continuous quality control including the use of standards for the studied polymorphisms as well as blanks for detecting contamination. The analysis should include methods that can identify genetic variation such as copy number polymorphisms.

6 EVALUATION OF THE CLINICAL CONSEQUENCES OF GENETIC DIFFERENCES IN DRUG SUBSTANCE EXPOSURE

If relevant PG-related differences are present for a medicinal product, the presentation of the PG/PK results should include a clear description of the alleles studied from biological and genetic perspectives, and a presentation of the PK or clinical parameters studied using appropriate statistics. The assessment of clinical consequences of any observed difference in drug exposure in a subpopulation should be based on several factors, such as:

- the magnitude of the difference in exposure,
- the relationship between drug exposure and clinical effects/adverse effects,
- the severity of the possible adverse events and clinical consequences of loss of efficacy.

The assessment could be based on clinical dose-ranging studies, on PK/PD studies, and on clinical data obtained in the genetic subpopulation and the study population as a whole.
Absence of data on clinical consequences in genetic subpopulations observed or estimated to have a marked exposure difference should be justified and adequately reflected in the SPC.

7 SPECIAL CONSIDERATIONS RELATED TO DRUG-DRUG INTERACTIONS AND IMPAIRED OR IMMATURE ORGAN FUNCTIONS

Drug interactions
Genotyping of the population included in an interaction study is recommended when PG is expected to affect the PK of any of the active substances. Depending on the question investigated, directed inclusion or exclusion of specific genotypes may be useful.

If well known major elimination pathways are absent in a subpopulation, the consequences of an inhibition of parallel pathways should be considered. The magnitude of such an interaction can be difficult to determine in the absence of an in vivo interaction study. However, a "worst case" scenario can usually be estimated. If the safety consequences of the interaction are predicted to give an unacceptable risk-benefit, or if sufficient safety data is lacking at predicted exposures, an interaction study in the subpopulation may be needed to reach satisfactory treatment recommendations.

The effect of active substances, that are enzyme or protein inhibitors or inducers, may also be different if the contribution of an enzyme is absent in a subpopulation. The consequences of inhibition of a protein in a population with a lower but not abolished activity of that protein should also be considered.
In case of induction, the net result will depend on the degree of induction -if any- of the parallel pathway. This should be considered especially when a dose recommendation for a certain drug-combination is studied and evaluated.

An increased systemic exposure in genetic subpopulations may lead to more pronounced effects of the investigated drug on other drugs. This should be considered and if necessary reflected in the SPC.

Impaired or immature organ function
The consequences of impaired organ function may be different in genetically different subpopulations. This applies mainly if the main elimination pathway (e.g. renal excretion) in the genetic subpopulation is markedly affected by impaired organ function. This should be discussed by the applicant as well as the need for such information in the SPC.

The enzymes and transport proteins involved in the PK of a drug substance may be quantitatively and qualitatively different in paediatric patients than in adults as a consequence of developmental changes in gene expression. The most marked differences are expected in newborn infants, infants and toddlers (0-2 year-old children).

In the very elderly patients PG related differences in metabolism may occur and have an impact due to impaired functionality of system/organs; limited knowledge is available at present.

8. TREATMENT RECOMMENDATIONS BASED ON GENETICALLY DETERMINED DIFFERENCES IN EXPOSURE

Dose recommendations

If there is a need for a dose adjustment, several routes can be applied:

I) Dose titration regardless of genotype
Differences in exposure in genetic subpopulations may be managed by dose-titration in all patients based on safety and/or efficacy markers, or on Therapeutic Drug Monitoring (TDM). If this approach is chosen, the applicant should show that the titration schedule is suitable for the specific subpopulation(s) known to have genetically caused variations in PK as well as for the general patient population.

II) Dosing based on genotype or phenotype
If dose titration is not desirable or feasible and if the safety or efficacy consequences of the exposure difference in the subpopulation are considered a major concern, the phenotype, e.g. based on genotyping, should be carefully ascertained before initiation of therapy.

III) Optional gene based dosing
If variability in drug action is undesirable, e.g. with respect to adverse events affecting quality of life, phenotype based dosing is highly recommended. In such cases the option of improving the benefit/risk via phenotyping- or genotyping prior to exposure should also be mentioned in the SPC.

Other labelling consequences

In general, the available data should be presented in relevant sections of the SPC. This may include sections 4.2, 4.3, 4.4, 4.5, 4.8, 5.1 and 5.2.

In case a suitable dose may not be recommended based on available data, or if other recommendations are more appropriate, this should be reflected in the SPC, e.g. as warnings, contra-indications, etc.

Well-documented functional polymorphisms that have not been studied because of their rare appearance should be reflected in the SPC if they are likely to influence drug exposure to a clinically relevant extent.

Information about the PK in different genetic subpopulations and, if available and relevant, differences in adverse event profile should be included in the SPC.

The frequencies of the alleles of interest in different populations, especially if the allele in question is rare in many populations, should briefly be presented in the SPC.