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Evaluation of Medicines for Human Use

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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

CONCEPT PAPER ON THE DEVELOPMENT OF A GUIDELINE ON THE USE OF PHARMACOGENOMIC METHODOLOGIES IN THE PHARMACOKINETIC EVALUATION OF MEDICINAL PRODUCTS

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1. INTRODUCTION

In recent years there has been a rapid development regarding our understanding of the genetics behind interindividual differences in drug response. This development encompasses the area of pharmacogenomics (PG) where interindividual variability in genes encoding drug transporters, and drug metabolising enzymes affects the systemic and target organ exposure of pharmacologically active substances, thereby affecting the efficacy obtained of drug treatment as well as the occurrence of adverse drug reactions. 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).

With respect to pharmacokinetic (PK) aspects, the highest abundance of genetic polymorphism is registered at the level of drug metabolism where approximately 40 % of phase I metabolism of clinically used drugs is catalysed by enzymes with polymorphisms known to have a marked impact on their function *in vivo* . Well known variable enzymes in this respect are the cytochrome P450 enzymes CYP2D6, CYP2C9, and CYP2C19. With regard to phase II enzymes, the genetic variability of UDP-glucuronosyltransferases, N-acetyltransferase-2 and some methyltransferases have been shown to play a role in the interindividual variability in PK. Among the drugs with current pharmacogenomic labels, the metabolising enzymes are in a majority accounting for 80 % of such labels. Finally, in recent years, striking examples have been published on the possible contribution of specific polymorphism in drug transporters to the distribution, efficacy and safety of medicinal products.

At present, an increasing fraction of drugs selected for development are metabolised by enzymes, for which there is very little knowledge on the impact of pharmacogenetics. New technologies, like the whole genome wide association studies (GWAS) methodology, have already been shown to be informative regarding the genetic basis for interindividual differences in drug distribution and adverse reactions and are already to some extent incorporated in clinical development programs. This development will lead to an accelerated increase of our knowledge on genetic variations in genes affecting drug pharmacokinetics and it is plausible that e.g., the GWAS technology will be an integrated technique during drug development for studying the genetic basis for interindividual differences in drug action.

2. PROBLEM STATEMENT

A Reflection paper on the use of pharmacogenetics in the pharmacokinetic evaluation of medicinal products (EMEA/128517/2006) was published by the EMEA in May 2007. Since the drafting of this Reflection paper, progress in the field has been considerable. In light of the evolution and broad acceptance of genotyping methods, as well as increased experience in the use of such pharmacogenomic methodologies during drug development, it was considered appropriate to update and align this progress in a Guideline on this topic.

3. DISCUSSION (ON THE PROBLEM STATEMENT)

Since the issuing of the Reflection paper in this topic progress in the field has continued at a good pace. Presently, pharmacogenetic sampling and analysis is included in the majority of the clinical development programs of new medicines. Also for medicinal products that are already marketed, useful pharmacogenomic information has become available. In order to discuss this progress, a joint EFPIA-EMEA workshop was held in London in December 2008. Based on the feedback obtained during the workshop, it was decided that a new Guideline on the use of Pharmacogenomic methodologies in Pharmacokinetic studies, in consultation with the various stakeholders, should be made.

The fundamental issues to be discussed in a proposed CHMP Guideline is how to implement pharmacogenetics affecting PK in drug development, how the pharmacokinetic variability arising from pharmacogenetic differences may best be determined, how to assess clinical relevance of the pharmacokinetic differences and recommendations on how to reflect these data in the labelling. This concept paper identifies issues that may need to be further addressed in the proposed CHMP guideline.

The main additional topics to be addressed in the proposed Guideline as compared to the Reflection paper are:

- Clarifications regarding how and when to apply genotyping during clinical development.
- Data needed for evaluating the clinical relevance of a pharmacogenetic effect on drug exposure as well as the benefits of applying genotyping during clinical use.
- Recommendations regarding pharmacokinetic studies investigating the effect of polymorphisms at transporter level.
- Guidance on specific technical aspects to be considered in assessing clinically relevant polymorphism (e.g. impact of the different allelic variants).

4. RECOMMENDATION

The PGWP and EWP-PK recommend drafting of a Guideline on the use of pharmacogenomic methodologies in pharmacokinetic studies.

5. PROPOSED TIMETABLE

It is anticipated that a draft Guideline will be available 9 months after adoption of the concept paper and will be released 6 months for external consultation, before finalization within 6 months.

6. RESOURCE REQUIREMENTS FOR PREPARATION

Development of the guideline will be led by the PGWP and the EWP-PK subgroup. A coordinating team will be appointed with representation from the above mentioned parties. Other relevant working parties, e.g. SAWP and external parties will be consulted as needed.

Drafting work will be conducted primarily by email and teleconferences. The PGWP and EWP-PK group will discuss draft versions also at their regular meetings.

7. IMPACT ASSESSMENT (ANTICIPATED)

It is important to keep the guidance up-to-date in the currently rapidly moving field of pharmacogenomic investigations. The guideline will provide expanded and improved guidance for both Pharmaceutical Industry and Regulatory Authorities regarding the application of pharmacogenomic methodologies in pharmacokinetic studies of medicinal products.

8. INTERESTED PARTIES

EMEA: EWP-PK, SAWP.
External consultation: pharmaceutical industry and academic and professionals networks.

9. REFERENCES

1. CHMP position paper on terminology in pharmacogenetics (EMEA/CPMP/3070/01).
2. Understanding the terminology used in pharmacogenetics (EMEA-3842-04).
3. Reflection paper on the use of pharmacogenetics in the pharmacokinetic evaluation of medicinal products (EMEA/128517/2006).