1 15 December 2011
2 EMA/CHMP/917570/2011
3 Committee for Medicinal Products for Human Use (CHMP)

4 Concept paper on key aspects for the use of 5 pharmacogenomic methodologies in the 6 pharmacovigilance evaluation of medicinal products

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Agreed by Pharmacogenomics Working Party	December 2011
Adoption by CHMP for release for consultation	15 December 2011
Start of public consultation	15 February 2012
End of consultation (deadline for comments)	15 May 2012

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Keywords	*Pharmacogenomics, Pharmacovigilance, Biomarkers, genomic variations*

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7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

1. Introduction

There is large variability in the response to drug therapy – in terms of both efficacy and safety. Some of the variation is related to inherited or non-inherited characteristics of the genome, i.e. genetic variations or activation/suppression of genome functions. These genetic variations may relate to drug disposition (pharmacokinetics) or drug action (pharmacodynamics). Consequently, there may be subsets of patients with a different benefit/risk profile.

Some genomic biomarkers may predict drug exposure or the risk status of a patient related to adverse drug reactions (ADRs). Genomic factors may play a role in the pathogenesis of both predictable and unpredictable ADRs as well as in clinical progression of diseases.

At the time of authorisation, information on the safety of a medicinal product is relatively limited due to many factors including the small numbers of subjects (including genetic subpopulations) in clinical trials, restricted inclusion criteria and restricted conditions of drug treatment. Furthermore, rare but serious ADRs (e.g. severe skin or hepatic reactions) may be identified late in the drug development phase or may only be discovered and characterised after authorisation and increased population exposure.

Identification of individuals at risk of developing ADRs, unexpected complications of the diseases or lack of efficacy (effectiveness) for a given drug will aid the development of strategies to optimise the clinical use of the medicines.

2. Problem statement

In spite of advances in the understanding of interindividual differences and their genetic basis, the occurrence of rare but serious ADRs or lack of efficacy/effectiveness are often identified at a late stage of drug development or long after drug approval. Knowledge and awareness of the presence or absence of a genetic variant may in many cases permit estimation of the likelihood of occurrence of ADRs or of effectiveness with the use of genetic information or tests. Currently, there is limited information on the utilisation of a genomic biomarker during follow up (post marketing) or on the effect of labelling with genomic information.

Therefore, guidance is needed on the evaluation of genomic influences during pharmacovigilance activities in order to inform and improve clinical use of specific treatments.

It is considered necessary to produce a guideline on the evaluation of pharmacogenomic specific issues in the conduct of pharmacovigilance.

3. Discussion (on the problem statement)

It is proposed to produce a guideline to further discuss the following aspects:

1. Systematic consideration of pharmacogenomic effects and the implications of genomic biomarker use in the target population in the risk management plan (RMP) for:
    a. Suspected/identified lack of efficacy / effectiveness of a relevant medicinal product related to the use of a genomic biomarker
    b. Safety concerns of a relevant medicinal product related to the use of a genomic biomarker

2. Early consideration of when, post authorisation genomic data may need to be monitored or collected to confirm appropriate dose and co-medications, as well as to provide information or advice based on identified genomic biomarkers.

3. Collection and storage of genomic material (e.g. DNA or other) during clinical trials and upon the occurrence of serious ADRs, lack of effectiveness post authorisation or unexpected worsening of the condition.

4. Methodologies for post authorisation safety studies and post authorisation efficacy/effectiveness studies regarding pharmacogenomic and Biomarker related issues (for adverse drug reactions and for lack of effectiveness) in the post marketing setting.

5. Consideration of the level and type of evidence for identification of signals, and how to report to the competent authorities (e.g. in RMP updates, periodic safety update reports (PSURs) – published studies etc.).

6. Consideration of risk minimisation measures depending upon the importance of the possible clinical implications.

7. Labeling issues

    a. What pharmacogenomic information to include in the product information (PI) and in which sections.

    b. Assessing the impact of information in the product information on the use of the medicinal products.

    c. Consideration of monitoring the effectiveness of genomic biomarker use in a clinical setting if there are requirements or recommendations in the product information on the use of genomic biomarkers.

The guidance should ensure that recommendations are clear and read across to existing CHMP/PGWP guidelines and Pharmacovigilance Guidelines (e.g. relevant GVP modules).

4. Recommendation

The Pharmacogenomics Working Party (PGWP) and Pharmavigilance Working Party (PhVWP) recommend to draft a Guideline on key aspects for the use of pharmacogenomic methodologies in the pharmacovigilance evaluation of medicinal product.

5. Proposed timetable

It is anticipated that a draft guideline will be available 9-12 months after adoption of the concept paper and will be released for 3 months of external consultation, before finalisation.

6. Resource requirements for preparation

Development of the guideline will be led by the PGWP and the PhVWP. A multidisciplinary drafting group will be appointed with representation from the above mentioned parties and of the virtual group on Summary of Product Characteristics (SmPC). Other relevant Committees or Working Parties, e.g. Scientific Advice Working Party (SAWP), and external parties will be consulted as needed.

Drafting work will be conducted primarily by email and teleconferences. The PGWP and PhVWP will discuss draft versions at their regular (plenary) meetings.

7. Impact assessment (anticipated)

The document is expected to provide guidance for both industry and Regulatory Authorities regarding the application of pharmacogenomic methodologies in the pharmacovigilance evaluation of medicinal products and to support the development of methodologies for monitoring of the effectiveness of genetic biomarker use in the clinical setting.

For stakeholders, including patients, learned societies and payers the guideline will increase transparency in the adoption of scientific opinions involving pharmacogenomics measures, thus facilitating the uptake of Personalised Medicines in clinical use.

8. Interested parties

External consultation: pharmaceutical industry, academic networks and patient organisations.