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Guideline on key aspects for the use of pharmacogenomics in the pharmacovigilance of medicinal products

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Executive summary

This guideline addresses the influence of pharmacogenomics on pharmacovigilance activities, including considerations on how to evaluate the pharmacovigilance related issues for medicinal products with pharmacogenomic associations, and how to translate the results of these evaluations to appropriate treatment recommendations in the labelling. Types of genomic biomarkers (BM) relevant for pharmacovigilance are illustrated with examples. Emphasis is given to the particular aspects of pharmacovigilance activities and risk minimisation measures in the risk management plan related to the use of medicinal products in genetic subpopulations.

1. Introduction

There is large interindividual 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. variations or activation/suppression of genome functions. These genomic variations may relate to drug disposition (pharmacokinetics, PK) or drug action (pharmacodynamics, PD) or to individual's susceptibility. Consequently, there may be subsets of patients with a different benefit-risk profile. Genomic factors may play a role in the pathogenesis of both predictable and idiosyncratic adverse drug reactions (ADRs).

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

The identification of subpopulations with either increased or decreased sensitivity to medicines due to genomic factors could provide important information that could be used to mitigate the risk of side effects and the risk of lack of efficacy in those subpopulations. Characterisation and categorisation of individuals based on genotype or phenotype to genomic subpopulations may lead to a significant increase in therapy benefit, decreased risks or both.

2. Scope

The scope of this guideline is to provide a framework and recommendations on how to evaluate the pharmacovigilance related issues associated with pharmacogenomic BMs, and how to translate the results of these evaluations to appropriate treatment recommendations in the labelling. This guideline also clarifies particular aspects of pharmacovigilance and risk minimisation measures relevant to medicinal products with pharmacogenomic associations. These should be considered together with the guidance provided by good pharmacovigilance practice.

Genomic issues related to disease risk and disease progression are not discussed in this guideline unless they are directly related to safety concerns and referred to in the risk management plan (RMP).

As technology is constantly evolving, a description on possible pharmacogenomic methodologies is outside the scope of this paper.

3. Legal basis and relevant guidelines

This guideline should be read in conjunction with all other relevant information included in current and future EU and ICH guidelines and regulations, especially:

- Guideline on the use of pharmacogenetic methodologies in the pharmacokinetic evaluation of medicinal products - EMA/CHMP/37646/2009
- Reflection paper on methodological issues with pharmacogenomic biomarkers in relation to clinical development and patient selection - EMA/CHMP/446337/2011
- Guideline on the evaluation of anticancer medicinal products in man - EMA/CHMP/205/95/Rev.4
- Reflection paper on pharmacogenomic samples, testing and data handling - EMEA/CHMP/ 201914/06
- Position paper on terminology in Pharmacogenetics - EMEA/CPMP/3070/01
- Rules governing medicinal products in the European Union Volume 2C Notice to applicants; A guideline on summary of product characteristics (SmPC) September 2009
- Note for Guidance on definitions for genomic biomarkers, pharmacogenomics, pharmacogenetics, genomic data and sample coding categories - EMEA/CHMP/ICH/437986/2006 (ICH Topic E15)
- Note for Guidance on genomic biomarkers related to drug response: context, structure and format of qualification submissions - EMEA/CHMP/ICH/380636/2009 (ICH Topic E16)
- Guidelines on good pharmacovigilance practices (GVP), e.g.:
  - Module V – Risk Management Systems
  - Module VI - Management and reporting of adverse reactions to medicinal products
  - Module VII – Periodic safety update report
  - Module VIII- Post-authorisation safety studies
  - Module IX – Signal management
  - Module XVI - Risk minimisation measures: selection of tools and effectiveness indicators
- Post-authorisation efficacy studies (PAES) when finalised.

4. Special characteristics of pharmacogenomics in pharmacovigilance

4.1. Types of genomic biomarkers

4.1.1. Biomarkers related to Pharmacokinetics (PK) and/or Pharmacodynamics (PD)

The analysis of BMs that influence the exposure levels of drug or metabolite(s), and thereby relate to dose/concentration-dependent effects has the potential to increase the safety and efficacy of drugs during therapy. The role of drug metabolising enzymes and transporter proteins most relevant for each drug from uptake to final elimination are recommended to be elucidated prior to approval of a new medicinal product. The same is expected for the more common polymorphic ADME (absorption, distribution, metabolism, and excretion) enzymes and the genomic variations that may influence drug-

drug interactions. In this respect, guidance on when and how to consider pharmacogenetic/pharmacogenomic studies in drug development is provided in the relevant guidelines (see Guideline on the use of pharmacogenetic methodologies in the pharmacokinetic evaluation of medicinal products - EMA/CHMP/37646/2009 and Guideline on the Investigation of Drug Interactions CPMP/EWP/560/95/Rev. 1).

However, depending on the state of the art knowledge at the time of drug development, only parts of the data might be available pre-authorisation and further investigation or studies might be necessary after approval of the product. The clinical phenotype clues and post-approval evidence leading to the identification of previously unknown pharmacogenomic BMs may be very diverse.

- Clopidogrel

An example of the identification of the impact a PK genomic BM can have on the benefits and risks of a medicine during the marketing of a medicine is the case of CYP2C19 and the use of clopidogrel as presented below.

Clopidogrel, a prodrug used for prevention of athero-thrombotic events in coronary artery and cerebrovascular disease or after stent implantation, is metabolised mainly by CYP2C19 to produce the active metabolite that inhibits platelet aggregation. In patients who are CYP2C19 poor metabolisers, less of the active metabolite is formed, which may result in serious clinical implications, e.g. stent thrombosis, myocardial infarction or even death. At the time of approval, the clinical impact of the active metabolite was not evident.

Out of a number of retrospective studies in the post-authorisation phase, some of them suggested that the combined group of patients with either intermediate or poor metaboliser status had a higher rate of cardiovascular events (death, myocardial infarction, stroke) or stent thrombosis compared to extensive metabolisers. In other studies, an increased event rate was observed only in poor metabolisers.

Based on relevant meta-analyses and the totality of available data, the product information of clopidogrel was updated in the EU to include information related to the increased risk of cardiovascular events in patients with reduced CYP2C19 function due to a genomic variant in the gene coding for the CYP2C19 protein. Similar effects on safety have been documented to occur when clopidogrel was used with CYP2C19 inhibitors, e.g. proton pump inhibitors.

Several other examples of the impact of pharmacogenomic variants in drug PK exist, e.g. tamoxifen and CYP2D6, warfarin and CYP2C9, and scientific evidence has been generated in the post-approval phase of the life-cycle of medicines.

- Warfarin

An example of the clinical impact a post-authorisation identification of PD-related genomic variants can have, is the case of vitamin K epoxide reductase (VKORC1) polymorphisms and the use of warfarin as presented below.

Warfarin, a vitamin K antagonist that inhibits the C1 subunit of the VKORC1 enzyme complex, has a well-known safety and efficacy profile. Certain single nucleotide polymorphisms (SNPs) in the VKORC1 gene have been associated with variable warfarin dose requirements. Patients with certain sensitising VKORC1 variants, e.g. 1639A at res992323, require a lower warfarin dose compared to wild-type carriers. Likewise, certain genetic variants in VKORC1, e.g. 9041A at rs7294, are associated with the requirement for a higher warfarin dose. Emerging data indicate interethnic differences exist; for example, the allele frequency for a VKORC1 promoter polymorphism associated with warfarin sensitivity is greater in Asians than Caucasians.

In addition to the variation in the VKORC1 gene that affects the pharmacodynamics of warfarin, genetic polymorphisms in CYP2C9 also affect the PK of this drug. The variant alleles, *CYP2C9*2* and *CYP2C9*3*, result in decreased clearance and higher blood levels of S-warfarin, the more potent enantiomer, increasing the risk of bleeding. Genotyping for these alleles has been shown to shorten the time to reach the required therapeutic anticoagulation state (International normalised ratio, INR).

Thus, VKORC1 and CYP2C9 gene variants, together with known non-genetic factors, can explain about half of the observed variability in warfarin dose requirements. Genotype information, when available, may thus assist in initial dose selection.

- Simvastatin

An example of a transporter BM, OATP1B1 (organic anion transporting polypeptide 1B1) encoded by the *SLCO1B1* gene, and its impact on the management of simvastatin-related myopathy is presented below.

Simvastatin is a cholesterol lowering agent and like other inhibitors of HMG-CoA reductase, is known to induce muscle adverse reactions including myopathy. This effect has been shown to be dose related.

Reduced function of hepatic OATP transport proteins can increase the systemic exposure of simvastatin and thus increase the risk of myopathy. Reduced function can occur as the result of inhibition of OATP by interacting medicines, e.g. ciclosporin or in patients who are carriers of the *SLCO1B1* c.521T>C genotype.

Patients carrying the *SLCO1B1* gene allele (c.521T>C) coding for a less active OATP1B1 protein have an increased systemic exposure of simvastatin and increased risk of myopathy. The risk of high dose (80 mg) simvastatin related myopathy is about 1 % in general, without genetic testing. Based on the results of a large clinical trial (the SEARCH trial), homozygote C allele carriers (also called CC) treated with 80 mg have a 15 % risk of myopathy within one year, while the risk in heterozygote C allele carriers (CT) is 1.5 %. The corresponding risk is 0.3 % in patients having the most common genotype (TT).

Based on available data, it was recommended in the EU labelling that where available, genotyping for the presence of the C allele should be considered as part of the benefit-risk assessment prior to prescribing 80 mg simvastatin for individual patients and high doses avoided in those found to carry the CC genotype. However, absence of this allele upon genotyping does not exclude that myopathy can still occur since only more than 60% of the myopathy cases could be attributed to the C variant in SLCO1B1.

Although *SLCO1B1* might also be involved in the occurrence of myopathy induced by other statin products, the strength of evidence is higher for simvastatin.

4.1.2. Genomic biomarkers associated with drug-induced toxicity risk status

Risk of serious ADRs not dependent on the level of drug exposure may relate to the subject's genomic variations in e.g. human leukocyte antigen (HLA) alleles.

Examples include HLA alleles and idiosyncratic reactions with abacavir, carbamazepine, and allopurinol. Studies demonstrating the predictive values of the genomic BM included both retrospective case-control studies and prospective clinical trials.

For example, carriers of the *HLA-B*5701* allele are at significantly increased risk of serious hypersensitivity reactions when exposed to the anti-retroviral agent abacavir, a nucleoside analogue reverse transcriptase inhibitor. A prospective randomised clinical trial demonstrated that about half of patients with the *HLA-B*5701* allele will develop a hypersensitivity reaction during the course of abacavir treatment with a relatively high positive predictive value (PPV) of 48% or 61% dependent on the methods for diagnosis. On the other side, almost no patients without the *HLA-B*5701* allele will develop this adverse reaction, i.e. high negative predictive value (NPV) of 96% or 100%. The pharmacogenomic association studies for abacavir were conducted in the post-authorisation period and resulted in an update of the summary of product characteristics (SmPC), incorporating the recommendation for *HLA-B*5701* allele screening prior to exposure or re-exposure to this agent.

Another example of genomic BMs predictive of immune mediated serious adverse reactions is the *HLA-B*1502* allele. Non-carrier status may predict the absence of severe skin reactions induced by carbamazepine. In this case the NPV is of high clinical significance although the PPV is low (see Annex 2). A strong association was noted between the absence of *HLA-B*15*02 and low incidence of Stevens-Johnson syndrome (SJS) or other cutaneous reactions in retrospective post-authorisation case-control studies. It is noted that the test for *HLA-B*1502* is most useful in certain Asian populations, e.g. Han Chinese and Thai patients, due to high NPV as well as a relatively high frequency of this allele in these populations. Clinical utility and effectiveness of the relevant risk minimisation measure, i.e. genotyping subjects prior to use and avoidance of carbamazepine in *HLA-B*1502* carriers, could be shown in a well-designed prospective study.

4.2. Special or vulnerable populations

Optimal drugs and drug doses for individuals may depend on a number of factors such as sex, age, body weight, ethnicity, genetic variation, co-morbidity, and drug–drug interactions. While all of these factors and their combinations may be important, the following examples are provided with reference to pharmacogenomics.

4.2.1. Ethnicity

Ethnic groups may differ in the prevalence of genomic BMs, in dosing needs and in the susceptibility to adverse reactions. It is not always feasible to gather information about these subpopulations during clinical trials. In such instances, reference to main genomic databases such as National Center for Biotechnology Information (NCBI), The Pharmacogenomics Knowledgebase (PharmGKB), and pharmacogenomic data collection in the post-authorisation phase have a potential to elucidate any association with genomic BMs to improve the benefit-risk balance of the medicinal product in ethnic subpopulations.

4.2.2. Impaired or immature organ function and age

The consequences of impaired renal function may be different in genetic subpopulations. This applies, e.g., if renal excretion is of increased importance in the genetic subpopulation. One example is the case of codeine metabolism in CYP2D6 ultra-rapid metabolisers (UM), who will form more active metabolites such as morphine and morphine-6-glucuronide. The latter is eliminated through the kidney. Higher plasma concentration of this active metabolite may be expected in CYP2D6 UM patients with renal impairment and they may thus experience opioid intoxication. If in addition the patient is taking concomitant medications that inhibit the alternative elimination pathways, the risk for adverse reactions may be further increased as a result of active substances accumulated.

The exposure to active substances resulting from impaired organ function in the genetic subpopulation should be estimated. Clinical consequences should be discussed and implemented in the labelling based on the available safety data, as appropriate.

- Paediatric populations

In some cases, the effect of age on the impact of genetic polymorphisms should be considered. E.g., the enzymes and transport proteins involved in the PK of a drug substance may be different in paediatric patients compared to adults as a consequence of different regulation of gene expression. Such differences are mainly expected in newborns, infants and toddlers (0-2 year-old children), e.g. CYP3A7 expression predominantly in newborns, and post-natal increase in CYP2C9, 2C19 and 3A4 expression in the first year after birth.

Therefore, if a significant impact of a genetic polymorphism on the PK of a medicine and/or the risk for adverse reactions has been established in adults, the potential consequences and justifications for conducting a study in the paediatric population should be further considered (see Guideline on conduct of pharmacovigilance for medicines used by the paediatric population EMEA/CHMP/PhVWP/235910/2005).

Opioid intoxication including fatal outcome has been reported in breast fed children of mothers receiving opioids who are CYP2D6 UMs. Therefore relevant information regarding the importance of genomic factors for pregnancy and lactation has been included in the labelling for codeine.

- Geriatric populations

Special considerations should be given to the impact of genetic polymorphisms on adverse reactions in older patients, often resulting from drug-drug interactions in view of poly-medication, multiple morbidities and frailty in this age group.

Genomic BMs seem to be of special relevance for the patients on polypharmacy. Genetic variations are therefore considered to be an important effect modifier of the occurrence of drug-drug interactions leading to subsequent adverse drug reactions in susceptible individuals. Further investigations about the significance of genomic BMs on reduction of safety risks in patients taking multiple medicines should be encouraged. This includes both testing for polymorphic metabolic enzymes and drug transporters with the influence on drug disposition in patients using interacting medicines.

5. Implementation of pharmacogenomics in pharmacovigilance

5.1. Risk Management Plan (RMP)

5.1.1. Safety Specification

The purpose of the safety specification in the RMP (see GVP Module V) is to provide a synopsis of the safety profile of the medicinal product(s) in the intended population as described in the approved Summary of Product Characteristics, e.g. in the therapeutic indications, or in the contraindications section, and should include what is known and areas of uncertainty about the medicinal product(s).

It is desirable to have data regarding relevant genomic BMs relating to efficacy or safety of a new medicinal product, including patient selection or dose specification for genomic subpopulations, available at time of marketing authorisation.

Safety specification of RMP should discuss important identified or potential risks or missing information related to the use of the medicinal products in the target population and potential off-label use. Reference to pharmacogenomics should be made when relevant data or evidence is available. The aspects indicated below should be considered.

- Genomically defined populations

The safety profile in populations defined by a known and clinically relevant genomic BM should be evaluated taking into account both investigational studies and literature review.

In case the entire development programme has been focussed on enriched clinical studies enrolling subjects or patients with well identified specific genomic variations, the ability to extrapolate the findings (efficacy and safety) to the general population or subjects with different genotype will need to be discussed. The discussion on important risks and missing information should include the potential impact of the medicine in the extended populations and potential for off-label use.

If a potentially clinically important genomic polymorphism has been identified but not fully studied in the clinical development program, it should be considered as missing information or a potential risk for the subpopulations. This should be reflected in the safety specification.

- Patients of different ethnic origins

Interethnic differences in drug efficacy and safety due to variations in prevalence of pharmacogenetic polymorphisms have been observed, e.g. higher prevalence of CYP2D6 poor metabolisers (PM) in northern Europeans than in southern Europeans or Asians; higher prevalence of *HLA–B*1502* in Han Chinese and Thai populations than several other ethnic groups. Therefore, information on ethnic origin may be relevant for the evaluation of efficacy and safety and for preventing adverse reactions or improving benefits in the target population.

Drug use in patients with different ethnic origins should be discussed in the RMP Safety Specification including the implications for PK, PD, efficacy and safety in the target population. This especially applies to situations where the initial use of the medicine was restricted to a certain ethnic group.

5.1.2. Pharmacovigilance plan

Safety concerns outlined in Safety Specification should be addressed in the Pharmacovigilance Plan. Pharmacovigilance activities can be classified as routine pharmacovigilance activities, e.g. handling of spontaneous reporting, signal detection and management, Periodic Safety Update Reports (PSURs) (see GVP VI, IX and VII), and additional pharmacovigilance activities, e.g. additional post-authorisation safety or efficacy (PASS/PAES) studies (see GVP VIII and XVI), which should be proportionate to the safety risks of the product within the intended clinical indications.

In specific situations, PASS and/or PAES may be needed to characterise the risks, including potential off-label use, to identify patients at risk or to optimise the benefit-risk balance. The questions to be addressed in the studies may relate to the identification and/or characterisation of genomic BMs, and their impact on patient selection, dose selection, and choice of concomitant medications. In addition the effectiveness of the risk minimisation measures can be evaluated.

Depending on possible scenarios, the following objectives of PASS/PAES may be considered

- to investigate a potential genomic BM and identify patients at risk:

    Scenarios:

- large interindividual variability or outliers in bioavailability following administration of a medicine, in particular where there is a narrow therapeutic index
- patients suffering from serious adverse reactions or lack of efficacy without known risk factors

- to confirm the impact of a genomic BM and optimise benefit-risk balance and risk minimisation measures:

  Scenarios:

  - uncertainties with respect to the efficacy of a medicinal product in genetically defined populations that could not be resolved prior to marketing authorisation and require further clinical evidence, e.g. BM status possibly important but data not available or not adequate or limited number of samples obtained in the population studied
- to study potential off-label use in a population outside the genomic BM defined indication
- to study effectiveness of risk-minimization measures for medicinal products with safety concerns where tests of genomic BMs are mandatory or recommended risk-minimisation measures

Pharmacovigilance planning with regards to genomic aspects should be considered early in drug development program, and continue into the post-marketing pharmacovigilance phase. Contents of the respective pharmacovigilance plan will vary by medicinal product and may e.g. be informed by:

- Results from (non-) clinical studies, e.g. on the contribution of metabolic enzymes and drug transporters to disposition of the medicine, and what is known about the drug target and PD
- Genome-wide association studies which are likely to be especially relevant to idiosyncratic toxicities

For details on signal detection and genomic data collection see section 5.2 below.

5.1.3. Risk minimisation plan

The types of risk minimisation measures are determined by the genomic BMs impact on the medicinal product's effects, risks and clinical outcome.

Routine risk minimisation measures include description of the genomic BM information in the labelling, e.g. when testing patients' BM status is warranted (see section 5.3.3 and Annex 1 below). Examples include:

- *HLA-B*5701* genotyping prior to the use of abacavir to minimize the occurrence of serious hypersensitivity reactions by avoiding the drug in *HLA-B*5701* carriers (risk status BM)
- CYP2D6 testing implications for alternative dosing, increased surveillance or avoidance of particular drugs in patients with a variant genotype in order to prevent ADRs related to increased drug or metabolite exposure (PK related genomic BMs)

When routine risk minimisation measures are not sufficient, additional risk minimisation measures used to guide appropriate patient selection or use of the medicine may be needed, such as, restricted access to medicinal products based on genotype or phenotype testing, patient registries, or additional educational materials to the prescribers or patients (see GVP Module XVI).

5.2. Genomic data collection and safety signal detection

Polymorphisms in genes encoding drug metabolising enzymes, such as CYP2C9, CYP2C19, and CYP2D6, drug transporters, such as SLCO1B1, and pharmacological targets, such as voltage-gated potassium channels related to congenital long QT syndromes, may lead to the occurrence of ADRs by the direct effect on a specific product or due to impact on drug-drug interactions.

It is a legal obligation that an effective pharmacovigilance system is in place in order to capture previously unidentified reactions related to specific genomic traits of individuals leading to idiosyncratic reactions.

In addition, pharmacogenetic influence on the occurrence of therapy failure can be investigated in the post-authorisation period.

Genomic information can be generated using data from the following sources:

1. Non-clinical studies: *in vitro* and *in vivo* data may provide direct and indirect indications of possible pharmacogenetic implications for the medicinal product. In particular mechanistic studies can provide valuable information for establishing the strategy for risk minimisation on solid scientific grounds.
2. Clinical studies: genomic sampling and testing as well as data collection of all study subjects and patients should be carried out, particularly in defined circumstances including exposure to drugs with narrow therapeutic index, or occurrence of unpredictable serious ADRs.
3. ADR case reports: valuable information can be generated from well-documented case reports; the relationship between the genetic BM (genotype or phenotype) and the clinical feature of adverse reactions could be evaluated. Spontaneous ADR reports related to possible genetic polymorphisms can be an important data source for signal generation or risk evaluation. Well-documented case reports may support product information change and/or trigger pharmacogenetic research.
4. Epidemiological studies: Genomic information linked to clinical data may be found in a number of sources, including clinical trials, cohort studies, case-control studies, registries, cross-sectional and longitudinal studies on public health databases. Coherence and eligibility of the sources of genomic information will need to be carefully evaluated prior to inclusion in any analyses.

The following post-authorisation activities are recommended for genomic data collection and safety signal detection:

- The marketing authorisation holder (MAH) should put in place a pharmacogenomic surveillance system including information tools, processes and studies to ensure that genomic BM testing is performed:
  - as required in the labelling to ensure the proper use of medicines for which the therapeutic indication and contraindication is determined by a genomic BM.
  - as recommended when, because of narrow therapeutic index, dosing is adjusted by the use of a genomic BM, to carefully monitor the patients.
- Collection of genomic samples, to further investigate a genomic BM, is recommended, when patients experience serious ADRs or lack of effectiveness, especially in the initial post-authorisation period, so that e.g. genomic characteristics from such patients could be compared with those of patients without these safety or efficacy concerns. Relevant biobanks should be identified, to make use of the existing infrastructure, and ultimately combine data from different biobanks.

Measurement of drug concentrations in post-authorisation clinical studies in patients who experience serious ADRs may provide useful information.

- Sampling of genomic material as part of pharmacovigilance activities in a product-specific RMP can be considered.

Collaborative actions should be promoted to gather adequate quality and amount of data, e.g. via a consortium (biobanking-) based approach involving MAHs, diagnostics industry, professional societies, research centres, academia, and regulatory authorities. Collecting genomic BM information from academic pharmacoepidemiological network databases may be explored. Internationally recognised pharmacogenetic/pharmacogenomic terms should be used for data mining or data presentation including those that are included in the medical dictionary for regulatory activities (MedDRA). Relevant literature should be screened for identification of signals. Inclusion of relevant information in the labelling or as part of the RMP should be performed as warranted. Reporting to regulatory agencies is expected if the findings fulfil the criteria for signals or emerging safety issues (see GVP VI).

It is encouraged that any relevant scientific findings emerging from the above activities should be aimed for public dissemination.

5.3. Risk Evaluation, level of evidence and recommendations

5.3.1. Risk evaluation and/or benefit-risk evaluation

Identified signals are evaluated according to the general process of signal management (see GVP module IX).

In PSURs (see GVP Module VII) relevant discussions regarding pharmacogenomic information should be placed in the section of “signal and risk evaluation”. Usage data and characterisation of benefits and risks in genomic BM based subpopulations should be presented, including the clinical utility or usefulness of the genomic BM.

Evaluation of data may relate to the strength of an association between a genomic BM, measured with a validated test method, and a safety concern, to severity/magnitude of the effect, and to patient ethnicity.

For the evaluation of genomic BMs related to idiosyncratic reactions, it is essential to identify and precisely define the clinical variables of the respective reaction. Genetic variants and their frequencies in relevant ethnic populations should be considered. When evaluating the performance of the BM, prospective studies are required and the sensitivity and specificity of the testing method should be presented. The PPV and the NPV of the testing method should be calculated, if relevant in different populations.

For the evaluation of genomic BMs related to PK or PD, the clinical variables may include level of drug concentrations, particular toxicity or lack of efficacy. The potential differences regarding the PK/PD related clinical variables and genomic BMs in different ethnic populations should be considered. When evaluating the predictive value of the genomic BM, the sensitivity and specificity of the testing should be presented.

It should also be considered that the clinical phenotype cannot always be predicted by genotype testing, especially in the case of polymorphic metabolising enzymes and transporters, due to multiple reasons including different food intake and/or concomitant medications. It might also be explained by not detected presence of rare variants in the gene of interest. Assessing the metabolic phenotype, e.g.

by measuring the plasma concentration of the drug and/or metabolites, should be considered. In clinically relevant and well defined cases the genomic BM may help optimising dosing.

When evaluating the value of genomic testing data sources, level of evidence, types of studies, methodology adopted, and consistency of the results should be considered. For recommendations on genomic testing, the presence or absence of therapeutic alternatives should be considered. The potential impact, e.g. risk increase, for patients with the certain genotype should be presented in relative as well as absolute terms where possible.

5.3.2. Level of evidence

For the successful adoption of genomic BM testing into clinical practice and public health, clinical validity and utility of an identified BM and the corresponding test should be demonstrated.

Clinical validity refers to the accuracy with which a test detects or predicts a given phenotype, i.e. clinical disorder or outcome. Clinical utility refers to the net balance of risks and benefits associated with using a test in routine practice, including its ability to inform clinical decision making, prevent adverse health outcomes and predict outcomes considered important to patients and other stakeholders.

In general, the ACCE model process (analytic validity, clinical validity, clinical utility and associated ethical, legal and social implications) that includes collecting, evaluating, interpreting, and reporting data about genetic testing, should be considered (see ACCE Model Process for Evaluating Genetic Tests, Centers for Disease Control and Prevention).

Information relating to genomic BMs and their potential effect on drug therapy may arise late in drug development when a number of clinical trials are completed or during post-authorisation. When data is analysed retrospectively to create evidence, there are certain caveats and requisites for its evaluation. Ideally data should be derived from well conducted randomised clinical trials, where the genomic BM status and the clinical information are available from the majority of subjects and represent the population of interest to avoid selection bias. A retrospective analysis should be pre-planned. In the post-authorisation phase, when signals are identified, replication of the association from different datasets adds significant value. Isolated retrospective observations are expected to provide confirmatory evidence whenever clinically and ethically appropriate.

The impact of the genomic BM findings on labelling guidance will depend on the relevance and importance of the associated clinical consequences.

5.3.3. Inclusion of information and recommendation in the product labelling

Inclusion and positioning of genomic information in the product labelling and therefore impact on clinical use and pharmacovigilance activities will be guided by the overall benefit-risk balance, magnitude of the genomic BM effect in specific genomic subpopulations, and the strength and conclusiveness of evidence. In addition, the seriousness of the adverse reactions, the underlying disease, therapeutic alternatives, dose dependency, idiosyncratic effects, and potential interactions with other medicinal products, need to be considered. Labelling should consider public health impact on the overall population and subsequently in specific genomic subpopulations.

Pharmacogenomics related information should be considered in the product labelling, in case an impact on the benefit-risk balance in a specific genomic subpopulation is identifiable by a genomic BM or set of

markers. Evidence should be sufficiently detailed and clear in the labelling. Risks and/or benefits in the subpopulation should be defined with guidance for the health care professional.

Evidence based recommendations and/or information in the labelling regarding pharmacogenomic testing can be classified as 1) mandatory, 2) recommended, or 3) for information.

1. Pharmacogenomic testing **mandatory**: Genomic testing in routine practice is supported by evidence and should be reflected in the Therapeutic Indication section of the label, and in other sections as relevant.
2. Pharmacogenomic testing **recommended**: Genomic testing may provide information guiding the use of the medicinal product or monitoring patients. The information is usually provided in the Posology or Warning/Precautions sections of the label and in other sections as relevant. In this case the evidence is not essential for the safe and efficacious use of the medicine.
3. Providing **information**: Current evidence does not allow making recommendations, however, providing the information may enable clinical decision making at individual level.

This classification will depend on the strength of evidence available and on the expected consequences for the efficacy and safety (see Guideline on the use of pharmacogenetic methodologies in the pharmacokinetic evaluation of medicinal products - EMA/CHMP/37646/2009).

Information on where genomic BM information should be indicated in the labelling, is included in Annex 1.

Examples regarding pharmacogenomic data evaluation and reflection in the labelling are provided in Annex 2.

5.3.4. Effectiveness of the risk minimisation measures

Evaluation of the effectiveness of risk minimisation measures is required. It may include specific studies requested through the RMP (see GVP Module XVI), e.g. to investigate whether a genomic BM guided use of a medicinal product has been effective or not.

It is important to assess whether genetic testing may have had unintended (clinical) consequences. It might be necessary to assess the impact of including information in the labelling in terms of clinical actions, e.g. are there changes how the medicine is used, are the recommendations followed particularly if not mandatory or what is the impact, if any, of adding information to the labelling, i.e. what are the impacts on clinical decision making.

An example of a study evaluating the effectiveness of risk minimisation measures is the study on *HLA-B*1502* allele screening before starting carbamazepine treatment in Han Chinese.

Risk minimisation measures might be not effective for the following reasons:

- the risk minimisation measure recommendations are not realistic / feasible
- the testing method used to investigate the genomic BM was not appropriate
- the risk minimisation measures are not understandable / clear
- the risk minimisation measure impact on clinical decision making is not clear
- the risk minimisation measures recommendations are not implemented (poor adherence and compliance)

Definitions and abbreviations

Definitions (For pharmacovigilance related terms GVP Annex I on definitions is referred to)

Active metabolites: metabolites that are involved in efficacy and/or safety.

Allele: one or more alternative forms of a gene that are found at the same place on a chromosome.

Clinical phenotype: A single or combination of disease attributes that is related to a genotype.

Gene: a locatable region of genomic sequence, corresponding to a unit of inheritance.

Genetic subpopulation: subdivision of the whole population, with common, distinguishing genetic characteristics. These characteristics may include both the phenotype, e.g. poor metaboliser, as well as the genotype, e.g. *CYP2D6*4*.

Genomic BM: a measurable DNA and/or RNA characteristic that is an indicator of normal biologic processes, pathogenic processes, and/or response to therapeutic or other interventions. (ICH15)

Pharmacogenetics (a subset of pharmacogenomics (PGx)): the study of variations in DNA sequence as related to drug response (ICH15). CIOMs VII (2005): Pharmacogenetics is defined as the study of inter individual variations in DNA sequence related to drug disposition (pharmacokinetics) or drug action (pharmacodynamics) that can influence clinical response.

Pharmacogenomics: the study of variations of DNA and RNA characteristics as related to drug response (ICH15). CIOMs VII (2005): Pharmacogenomics is defined more broadly as the application of genomic technologies to elucidate disease susceptibility, drug discovery, pharmacological function, drug disposition and therapeutic response.

Pharmacovigilance (PhV): the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem (see WHO).

Phenotype: The observable physical or biochemical characteristics of an organism, as determined by both genetic makeup and environmental influences.

Polymorphism: When two or more clearly different phenotypes exist in the same population, the population is called polymorph.

Abbreviations

ADME: absorption, distribution, metabolism, and excretion

BM: biomarker

DNA: Deoxyribonucleic Acid

GVP: Good Pharmacovigilance Practice

NPV: negative predictive value

PAES: post-authorisation efficacy studies

PASS: post-authorisation safety studies

PD: pharmacodynamics

PI: product information

PK: pharmacokinetics

PM: poor metaboliser

PPV: positive predictive value

PSUR: Periodic Safety Update Report

RMP: Risk Management Plan

RNA: Ribonucleic Acid

SJS: Stevens–Johnson syndrome

SNP: Single Nucleotide Polymorphism

SmPC: Summary of Product Characteristics

TEN: Toxic Epidermal Necrolysis

UM: ultra-rapid metaboliser

VKOR: vitamin K epoxide reductase

References

Centers for Disease Control and Prevention (CDC) ACCE Model Process for Evaluating Genetic Tests: http://www.cdc.gov/genomics/gtesting/ACCE/

EMA home page - Pharmacogenomics guidance: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000411.jsp&mid=WC0b01ac058002958e

EMA home page – Reflection paper on pharmacogenomic samples, testing and data handling: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003864.pdf

Annexes

Annex 1. Relevant pharmacogenomic biomarker information may be included in SmPCs in line with the SmPC Guideline

Section 4.1 Therapeutic Indication: "*If the product's indication depends on a particular genotype or the expression of a gene or a particular phenotype, this should be stated in the indication.*"

Section 4.2 Posology: "*Dosage adjustment or other posology related information in specific patient groups should be stated where necessary,* (…): *patients with a particular genotype; with cross-reference to other relevant sections for further detail as appropriate.*"

Section 4.3 Contraindications: "*Situations where the medicinal product must not be given for safety reasons*" to individuals with "*a particular genotype*"

A contraindication could refer to a genotype or a phenotype, if more appropriate.

Section 4.4 Special warnings and precautions for use: "*Subjects or patients with a specific genotype or phenotype might either not respond to the treatment or be at risk of a pronounced pharmacodynamic effect or adverse reaction. These may arise because of non-functioning enzyme alleles, alternative*

metabolic pathways (governed by specific alleles), or transporter deficiencies. Such situations should be clearly described if known."

This should include any information on the prevalence of particular phenotype or genotype in any relevant ethnic population that warrants an alert for a risk in response to a drug therapy (in terms of either efficacy or safety) in that population. Cross-reference to other sections such as 4.8 or 5.2 should be added as appropriate.

Section 4.5 Interaction with other medicinal products and other forms of interaction: "*If there are patient groups in which the impact of an interaction is more severe, or the magnitude of an interaction is expected to be larger e.g. patients with decreased renal function (in case the parallel pathway is renal excretion), paediatric patients, elderly etc., this information should be given here.*" "If interactions with other medicinal products depend on polymorphisms of metabolising enzymes or certain genotypes, this should be stated."

Section 4.6 Pregnancy and lactation: "*Any information regarding the potential effect of genomic factors in pregnancy or in breastfeeding infants may be provided here*." Cross-reference to section 5.2 may be added as appropriate.

Section 4.8: Undesirable effects: *"This section may include information on any clinically relevant differences (i.e. in nature, frequency, seriousness or reversibility of adverse reactions, or need for monitoring) specifically observed in other special populations such as elderly, patients with renal impairment, patients with hepatic impairment, patients with other diseases or a specific genotype. Cross-reference to other sections such as 4.3, 4.4 or 4.5 may be added as appropriate." "Adverse reactions may also be related to genetically determined product metabolism. Subjects or patients deficient in the specific enzyme may experience a different rate or severity of adverse reactions. This should be mentioned and where relevant correlated with data from clinical trials."*

Section 4.9 Overdose: "*If applicable, counteractive measures based on genetic factors should be described.*"

Section 5.1 Pharmacodynamic properties: "*Any relevant pharmacogenetic information from clinical studies may be mentioned here. This should include any data showing a difference in benefit or risk depending on a particular genotype or phenotype.*"

Section 5.2 Pharmacokinetic properties: "*Variations with respect to (…) polymorphic metabolism (…). If the influence on pharmacokinetics is considered to be clinically relevant, it should be described in quantitative terms (with cross-reference to 4.2 when applicable)*." The frequencies of the alleles of interest affecting pharmacokinetics in ethnic populations should be presented. If there is a need to add an alert for any specific ethnic population, a cross-reference to section 4.4 should be added as appropriate."

Annex 2. Examples – from data evaluation to labeling

Drug	Genomic biomarker	Allele frequency (ethnicity)	Issue-ADR (severity, frequency, etc.)	Prevalence phenotype	Risk of ADR	Data source (incl. study design, etc.)	PPV	NPV	Label (sections in SPC)
Abacavir	*HLA-B*5701* (all races)	6-8% in Caucasians, 1% in Asian populations	Hypersensitivity, Severe	6 - 8%	48% to 61% of patients with the allele vs 0%	Prosp. CT and others	55%	100%	4.1, 4.4

		and less than 1% in African populations			to 4% of patients without the allele				
Carbamazepine	*HLA-B*1502*	10% in Han Chinese and Thai populations, < 1% in e.g. European descent, Japanese and Koreans	SJS, severe	0.06 – 0.2%	3 % in Han Chinese with the allele vs 0% of patients without the allele	Case control, + prospective cohort	3%	100%	4.2 and 4.4
Carbamazepine	*HLA-A*3101*	2 to 5% in Northern European populations and about 10% in Japanese population	cADR, (less) severe	5%	26% of patients with the allele vs 3.8% of patients without the allele	Case control	42%	92%	4.4
Allopurinol	*HLA-B*5801* (Chinese/ Thai, and other)	Up to 20% in Han Chinese population, about 12% in the Korean population and 1-2% in Japanese or European origin	SJS/TEN (or cADR), severe Rare/very rare?	0.04%?	OR >300 in Chinese and Thai.	Case control	Low	40 -100%	4.4 and 4.8
Clopidogrel	*CYP2C19*2, *3*	*2: 15% in White, >20 % in Asian, 8% in blacks; *3: 0-<1 % in White, 5-10 % Asian, 0-2% in blacks.	Reduced levels of active metabolite in PMs with risk for reduced efficacy.	Approximately 2% in Caucasians, 4% in Blacks and 14% in Chinese are PMs.	Uncertain.	PK, retrospective, epidemio-logical studies; Meta-analysis	Unknown	Unknown	4.4, 4.5, 5.2
Celecoxib	*CYP2C9*2, *3*	*2: 15% in White, 2.9% in Asian; *3: 5.7% in White, 3.9%	High exposure in PMs		Unknown	PK study	Unknown	Unknown	4.2, 4.4

		Asian							
Tamoxifen	*CYP2D6*4* (Caucasians), *CYP2D6*10* (Chinese)	PM: 5-10% in White, 2-7% in Black, 0-5% in Asian	Cancer relapse and mortality increase, in PMs		OR <2	PK, retrospective study, (prospective CT), epidemio-logical studies	Unknown	Unknown	4.4, 4.5, 5.1
Simvastatin	*SLCO1B1 C allele*	CC carrier: 0-6% of patients.	Myopathy	1%	CC: 15%; CT: 1.5%; TT: 0.3%	Clinical trials	Unknown	Unknown	4.4, 5.2.