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Guideline on key aspects for the use of pharmacogenomic methodologies in the pharmacovigilance evaluation 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 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 (background)

There is large interindividual variability in the response to drug therapy – in terms of both efficacy and safety, mostly due to gene-environmental interactions. 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 sub-populations) 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 sub-populations with either increased or decreased sensitivity to medicines due to genomic factors could reduce both the risk of side effects and the risk of lack of efficacy in those sub-populations. Characterization and categorization of individuals based on genotype or phenotype to genomic sub-populations 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 biomarkers, 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).

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:

- ICH Note for Guidance Pharmacovigilance planning - CPMP/ICH/5716/03

- 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
- 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):
  - 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 (BM) related to Pharmacokinetics (PK) and/or Pharmacodynamics (PD)

The analysis of biomarkers 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 metabolizing enzymes and transporter proteins relevant for each drug from uptake to final elimination are expected to have been elucidated prior to approval of a new medicinal product. The same is expected for polymorphic ADME enzymes and the genomic variations that 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 "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 years after approval of the product. The clinical phenotype clues and

post-approval evidence leading to the identification of previously unknown pharmacogenomic biomarkers may be very diverse.

As an example of post marketing identification of a PK genomic biomarker with clinical impact on benefit risk of a medicine, the case of CYP2C19 and the use of clopidogrel is 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 (Mega et al. 2009). 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, it was not possible to determine the active metabolites.

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 postulated 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.

As an example of a PD-related genomic variant identified post-approval the impact of vitamin K epoxide reductase (VKORC1) polymorphisms and the use of warfarin is presented below.

Warfarin, a vitamin K antagonist that inhibits the C1 subunit of 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. Thus, different variants of VKORC1 sensitise individuals to warfarin are known, whereas disrupting mutations in VKORC1 may cause warfarin resistance. Emerging data indicating also interethnic differences in such effect exist.

In addition to the variation in VKORC1 gene that affects the pharmacodynamics of warfarin, genetic polymorphisms in CYP2C9 also affect PK of this drug. The variant alleles, *CYP2C9*2* and *CYP2C9*3*, result in decreased clearance and higher blood level 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 (INR, international normalized ratio) (Pirmohamed et al. 2013).

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 dose selection (Lenzini et al. 2010).

4.1.2. Genomic biomarkers associated with drug-induced toxicity risk status (e.g. human leukocyte antigen (HLA) alleles):

Serious reactions not dependent on the level of drug exposure (PK) or drug action (PD), may relate to patient risk status. Examples include HLA alleles and idiosyncratic reactions with abacavir, carbamazepine, and allopurinol. Various types of studies provided the evidence allowing regulatory

action. Studies evaluated to define the predictive values of the genomic biomarker included both retrospective case-control studies and prospective clinical trials.

Carriers of the *HLA-B*5701* allele are at significantly increased risk of serious hypersensitivity reactions when exposed to the anti-retroviral agent abacavir (Mallal et al 2008). In this prospective randomised clinical trial it is estimated that about half of patients with the *HLA-B*5701* allele will develop a hypersensitivity reaction during the course of abacavir treatment (with relatively high positive predictive value, PPV, of 48% or 61% dependent on the methods for diagnosis). On the other side, almost no patients who do not have the *HLA-B*5701* allele will develop the adverse reaction (high negative predictive value, NPV, of 96% or 100%). Of note, the pharmacogenomic association studies for abacavir were conducted in the post authorisation period and resulted in an update of the summary of product characteristics (SPC), incorporating the recommendation for screening for the HLA-B*5701 allele prior to exposure (or re-exposure) to this agent.

Another example of genomic BM predictive of immune mediated serious adverse reaction is HLA-B*1502 allele for which the non-carrier status may predict the absence of the most 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 Steven 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 (Chen et al. 2011). The importance of ethnicity and genomic BM status is also discussed in the next section.

4.2. Special or vulnerable populations

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

4.2.1. Ethnicity

Ethnic groups may differ in the prevalence of genomic biomarkers, in dosing needs and in the susceptibility to adverse reactions. However, it is not always feasible to gather information about these sub-populations during clinical trials due to a multitude of limitations and sometimes restriction by legislation. In such instances, reference to main genomic databases such as National Center for Biotechnology Information (NCBI), PharmacoGenomic Knowledge Base (GKB) and pharmacogenomic data collection in the post authorization phase have a potential to elucidate any association with genomic biomarkers to improve the benefit risk of the medicinal product in ethnic sub-populations.

4.2.2. Impaired or immature organ function and age

The consequences of impaired renal function may be different in genetically different subpopulations. This applies, e.g., if renal excretion is of increased relative importance in the genetic sub-population. One example would be in the case of codeine metabolism in CYP2D6 ultra-rapid metabolisers (UM), who will form more active metabolite 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 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 higher active substances accumulated.

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

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 young paediatric patients than in adults as a consequence of different regulation of gene expression. Such differences are mainly expected in newborn infants, infants and toddlers (0-2 year-old children), e.g. CYP3A7 expression in newborn, 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 drug substance and/or the risk for adverse reactions has been established in adults, the potential consequences in the paediatric population should be further considered.

Opioid intoxication including fatal outcome has been reported in breast fed children of mothers who are UMs. Therefore relevant information regarding the importance of genomic factors for pregnancy and lactation should be considered in the labelling.

Older patients

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.

5. Implementation of pharmacogenomics in pharmacovigilance

5.1. Risk Management Plan (RMP)

5.1.1. Safety Specification (identified / potential important risks, missing information)

The purpose of the safety specification in the RMP 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 Products Characteristics (e.g. therapeutic indications, or contraindications), and should include what is known and areas of uncertainty about the medicinal product(s).

Generally, it is expected 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 sub-populations, available at time of marketing authorisation.

In the safety specification of RMP, 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, should be discussed with reference to pharmacogenomics. The aspects indicated below should be considered.

- Genomic sub-populations

The safety profile in such population, e.g. sub-population identified by a known and clinically relevant genomic BM should be discussed.

In case the entire development programme has been conducted in 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 both within the pre-authorisation dossier and in the RMP including appropriate pharmacovigilance activities and/or specific risk minimisation measures. 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, this should be considered as missing information or a potential risk in the sub-populations.

This should be reflected in the safety specification.

- Patients of different ethnic origins

Inter-ethnic differences in drug efficacy and safety have been observed due to variations in prevalence of pharmacogenetic polymorphisms (e.g. the prevalence of CYP2D6 poor metabolisers (PM) is higher 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, especially in those situations where the initial use of the medicine was restricted to a certain ethnic group.

5.1.2. Pharmacovigilance plan (routine or additional activities)

Safety concerns outlined in Safety Specification should be addressed in the Pharmacovigilance Plan. Pharmacovigilance activities can be classified as routine pharmacovigilance activities (e.g. signal detection and management, and PSURs), and additional pharmacovigilance activities, e.g. additional post authorization safety or efficacy (PASS/PAES) studies (GVP VIII or other Guidelines), which should be proportionate to the risks of the product within the intended clinical indications.

When the genomic BM status directly influences PD or efficacy (i.e. efficacy of the drug is dependent on the biomarker status which identifies the intended target population) the relationship is likely to be well characterised during the pre-authorisation phase and therefore have significant impact on the risk minimisation activities, e.g. product labelling.

However, in other cases a genomic BM may be an indicator of either lack of efficacy or adverse reactions. It is important that the marketing authorisation applicant/holder has a strong scientific rationale behind the use of the product in both marker positive and marker negative subjects and should keep focus on characterisation of the genomic BM impact on the safe use of the product.

In specific situations, PASS/PAES may be needed to characterise the risks, to identify patients at risk or to optimise benefit-risk. The questions to be answered in the studies may relate to the identification of genomic BM, and their impact on patient selection, dose selection, and choice of concomitant medications taking into account sensitivity and specificity as well as PPV and NPV. In addition the effectiveness of the risk minimisation measures can be evaluated.

Details on signal detection and genomic data collection are referred to section 5.2 below.

5.1.3. Risk minimisation plan (routine or additional activities)

The type of risk minimisation measures depends upon the impact of the genomic BM on the medicinal product's effects, risks and the clinical implication.

The routine risk minimization measure includes description of the genomic BM information in the product information (see section 5.3.3 and Annex 1 below). For example, as appropriate, testing the patient for the BM status may be warranted, e.g. *HLA-B*5701* genotyping prior to the use of abacavir to minimize the occurrence of serious hypersensitivity reactions by avoiding the drug in the carriers. In the case of genomic BM related to PK, e.g. CYP2D6, avoid the use of CYP2D6 substrates in PM (or UM) to prevent the ADRs related to increased drug (or active metabolites) exposure. Alternatively, these patients may benefit from different dosage regimens.

Dependent on the situation, additional risk minimisation measures used to guide appropriate patient selection, such as, restricted access to the medicinal products based on specific (genotypic or phenotypic) tests, a patient registry, or additional educational materials to the prescribers or patients regarding important genomic BM information may be needed.

5.2. Signal detection and genomic data collection

Polymorphisms in genes encoding drug metabolizing enzymes, such as CYP2C9, CYP2C19 and CYP2D6 (PK level), drug transporters (PK and/or PD level) and pharmacological targets, e.g. voltage-gated potassium channels related to congenital long QT syndromes (PD level), may relate to the occurrence of adverse drug reactions either for the direct effect on a specific product or due to impact on drug-drug interactions.

The pre-authorisation evaluations should in principle have established the overall role of such pharmacogenomic influence related to dose response, and overall level of safety and efficacy.

Nevertheless, it is important that an effective pharmacovigilance system is in place in order to capture otherwise unidentified reactions related to specific genomic traits of individuals leading to the so called idiosyncratic reactions. Yet unidentified genomic BM influence on serious ADRs may be discovered from the post-authorisation experience.

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

Special attention should be given to ethical issues and informed consent related to the use of genomic samples and relevant clinical data for the purpose to address the genomic impact on the benefit risk balance of medicinal products in clinical use.

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

- Preclinical 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 in vitro in cells or isolated tissues can provide valuable information for establishing the strategy for risk minimization on solid scientific grounds.
- Clinical studies: Genetic testing of all subjects and patients participating in clinical trials is being increasingly considered, and in defined circumstances e.g. drugs with narrow therapeutic index, unpredictable serious ADRs, genomic data collection is recommended also for post-authorisation studies.
- ADR case reports: valuable information can be generated from well-documented case reports including information on the relationship between the genetic BM (genotype or phenotype) and the

clinical feature of the adverse reactions. Spontaneous ADR reports related to possible genetic polymorphisms could be an important data source for signal generation or risk evaluation. Well-documented case reports may lead to product information change and/or trigger pharmacogenetic research.

- Epidemiological studies: Genomic information directly or indirectly linked to clinical data may be found in a number of sources: clinical trials, ad hoc cohorts, case registries, and cross-sectional and longitudinal population samples.

  Various clinical and epidemiological study designs and methods are used to assess the possible association between drug induced ADRs and genomic BMs (see the following link: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000411.jsp&mid=WC0b01ac058002958e).

  In case of serious ADRs or lack of efficacy, the collection and storage of genomic material (e.g. blood, saliva, and tissue) may prove essential to elucidate the potential importance of genomic BMs (see the following link: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003864.pdf).

The following activities should be considered:

- Pharmacogenomic surveillance system: genomic biological samples should be collected prior to prescription of medicines for which the therapeutic indication and contraindication is determined by genomic BM, and when, because of narrow therapeutic index, dosing is adjusted by genomic BM.
- In addition, from every patient receiving a medication and experiencing serious ADRs or lack of effectiveness, it should be encouraged that genomic samples be collected especially in the initial post-authorisation period so that e.g. DNA traits from such patients could be compared with those of patients without those safety or efficacy concerns. On a case by case basis genomic material sampling might be part of product-specific RMP.
- Collaborative actions, such as a consortium (biobanking)-based approach involving MAHs, academia and regulatory authorities should be considered.
- To map pharmacogenomic risk factors for drug responses it is recommended to incorporate genomic data into databases with individual clinical phenotype. Collecting genomic BM information from academic pharmacoepidemiological networks databases may be explored as appropriate.
- Internationally recognized pharmacogenetic/pharmacogenomic terms (including those that are included in MedDRA) should be used for data mining or data presentation, as appropriate.
- Relevant literature should be screened for identification of signals.

5.3. Risk Evaluation, level of evidence and recommendations

5.3.1. Risk evaluation and/or benefit risk evaluation

The identified signals are further evaluated according to the agreed general process of signal management (GVP module IX).

In the PSURs (GVP Module VII) relevant discussions regarding the pharmacogenomic information should be made in the section of “signal and risk evaluation”, e.g. exposure data and characterisation

of risks/ benefits in genomic BM based sub-populations should be presented, including the clinical utility or usefulness of the genomic BM.

The 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. To be noted here is the consideration that while PPV is important for efficacy biomarkers, the NPV more commonly is important for the safety biomarkers (for the avoidance or minimisation of safety risks).

In general, the following aspects should be considered when evaluating safety genomic BM:

For the evaluation of genomic BM testing for idiosyncratic reactions (e.g. HLA alleles for drug induced hypersensitivity or cutaneous reactions) it is essential to first identify and precisely define the clinical variables (e.g. the adverse reactions and their clinical attributes e.g. severity) and their frequencies in relevant ethnic populations. Secondly, the genetic variants and their frequencies in relevant ethnic populations should be considered. When evaluating the performance of the BM, the sensitivity and specificity of the testing should be presented and the PPV and the NPV with the testing method chosen should be calculated (in different populations if relevant).

For the evaluation of genomic BM related to PK (e.g. polymorphisms in drug metabolising enzymes, such as CYP2D6, or transporters such as SLCO1B1) or PD, the clinical variables may include level of drug concentrations, in addition to lack of efficacy or particular toxicity. The potential differences regarding the PK/PD related clinical variables and genomic BM in different ethnic populations should be considered as appropriate. 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 phenotype cannot always be predicted from a genotyping test especially in the context of polymorphic metabolising enzymes and transporters because of e.g. food or concomitant medications. Therefore as relevant measuring metabolic phenotype (e.g. plasma concentration of the drug and/or metabolites) should be considered. Effects related to gene copy number should be considered. In clinically relevant and well defined cases the genomic BM may help optimal dosing.

Regarding the evaluation of data sources and level of certainty on the evidence, the 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 risk increase in patients with the genomic BM should be presented in relative as well as absolute terms.

5.3.2. Level of evidence

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

Clinical validity refers to the accuracy with which a test detects or predicts a given phenotype (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 (e.g. morbidity, mortality), and predict outcomes considered important to patients and their families.

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 (CDC: ACCE Model Process for Evaluating Genetic Tests).

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 post authorisation. When such retrospective evidence is gathered or presented, there are certain caveats/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 the subjects and represent the population of interest (to avoid selection bias), and the 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 will depend on the level of evidence and clinical relevance.

5.3.3. Inclusion of information and recommendation in the product information

Inclusion of pharmacogenetic information in the product information and its impact on pharmacovigilance activities will be guided by the overall benefit risk balance in specific genomic subpopulations, magnitude of the genetic / genomic biomarker effect and the level of evidence. In addition, the importance of contextual factors such as the seriousness of the adverse events and the seriousness and /or severity of the underlying disease being treated, and presence of therapeutic alternatives, needs to be considered. The evidentiary base should be characterised in the context of public health impact firstly in the overall population and subsequently in the target population of interest.

For example, if the pharmacogenomic information alters the risk benefit balance for treatment with a particular medicinal product in the target population identifiable by a biomarker or set of markers, such information should be included in the product information, which should be sufficiently detailed and clear to define the risks or benefits in the target population with guidance for the treating physicians. The information should include the details of the target population, impact on the risk benefit balance and if there are dose dependent or idiosyncratic effects and finally potential interactions with other medicinal products.

Evidence based information/recommendations regarding pharmacogenomic testing can be classified as 1) for providing information for clinical decision making, 2) recommended or 3) mandatory. This will depend on the strength of the data available and on the efficacy and safety consequences expected.

Information regarding the appropriate sections where genomic BM information should be indicated in the labelling, based on the SmPC guideline 2009, is included in Annex 1. Some examples regarding pharmacogenomic data evaluation and reflection in the labelling are included in Annex 2.

5.3.4. Effectiveness of the risk minimisation measures

Studies on the effectiveness of the risk minimisation measures related to genomic BM use should be considered, as appropriate.

Evaluation of the effectiveness of risk minimisation measures is necessary to establish whether the medicinal product use guided by the genomic BM has been effective or not; if not, a) is it because the recommendations are not followed or because the recommendations themselves are less than optimal; b) whether the testing method used was not appropriate or successful and if corrective actions are necessary. It is important to assess if the genetic test may have had unintended consequences. It might be necessary to assess the impact of including information in the SmPC in terms of clinical actions, e.g. are there changes in how the medicines are being used, are the recommendations being

followed particularly if not mandatory or what is the impact, if any, of adding information to the SmPC, i.e. what are the impacts on clinical decision making.

One 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. It was shown that identification of *HLA-B*1502* carriers and avoidance of carbamazepine in these subjects was strongly associated with a decrease in the incidence of carbamazepine induced SJS – Toxic epidermal necrolysis (TEN) (Chen et al. 2011).

Definitions and abbreviations

Definitions

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

Allele: DNA sequence at a given locus of a particular gene.

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 biomarker: 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 interindividual 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 drug-related problem. The aims of PhV are to enhance patient care and patient safety in relation to the use of medicines; and to support public health programmes by providing reliable, balanced information for the effective assessment of the risk-benefit profile of medicines (WHO).

Abbreviations

ADME: absorption, distribution, metabolism, and excretion

BM: biomarker

DNA: Deoxyribo Nucleic Acid

GVP: Good Pharmacovigilance Practice

NPV: Negative Predictive Value

PAES: post authorization efficacy studies

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

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EMA home page with lists of scientific guidance documents on pharmacogenomics: 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

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Annexes

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

Section 4.1: “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: “Special populations: patients with a particular genotype where dose is different in special populations or use is different with cross-reference to other relevant sections for further detail as appropriate.”

Section 4.3: Situations where the medicinal product must not be given for safety reasons to individuals with a particular genotype or phenotype should be stated in the contraindication.

Section 4.4: Subjects 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. This should be described as warnings or precautions.

Section 4.5: “Additional information on special populations. 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.”

Section 4.8: “e. <Other special populations> 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.”

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

Section 5.1: “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: Variations with respect to polymorphic metabolism should be described, if clinically relevant, 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.

555 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 and less than 1% in African populations	Hypersensitivity, serious	- 8%	48% to 61% of patients with the allele vs 0% to 4% of patients without the allele	Prosp. CT and others	55%	100%	4.1
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	cADR, (less)	5%	26% of patients with	Case control	42%	92%	4.4

		European populations and about 10% in Japanese population	severe		the allele vs 3.8% of patients without the allele				
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
Celecoxib	*CYP2C19*2, *3*	*2: 14-17% in White and Black, 30-34% in Chinese and Japanese; *3: <1 in White and Black, 5-9% in	High exposure in PMs		Unknown	PK study	Unknown	Unknown	4.2, 4.4

		Chinese and Japanese							
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

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