4 Guideline on key aspects for the use of pharmacogenomic
5 methodologies in the pharmacovigilance evaluation of
6 medicinal products
7 Draft

Draft Agreed by Pharmacogenomics Working Party	April 2013
Adoption by CHMP for release for consultation	20 December 2013
Start of public consultation	30 January 2014
End of consultation (deadline for comments)	30 July 2014

8
9

Comments should be provided using this template. The completed comments form should be sent to PGWPSecretariat@ema.europa.eu.

10

Keywords	*Pharmacogenomics, Pharmacovigilance, Biomarkers, genomic variations*

11

Guideline on key aspects for the use of pharmacogenomic methodologies in the pharmacovigilance evaluation of medicinal products

Table of contents

Guideline on key aspects for the use of pharmacogenomic methodologies in the
pharmacovigilance evaluation of medicinal products
EMA/281371/2013   Page 2/18

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

82 • Guideline on the use of pharmacogenetic methodologies in the pharmacokinetic evaluation of
83   medicinal products - EMA/CHMP/37646/2009

84 • Reflection paper on methodological issues with pharmacogenomic biomarkers in relation to clinical
85   development and patient selection - EMA/CHMP/446337/2011

86 • Reflection paper on pharmacogenomic samples, testing and data handling - EMEA/CHMP/
87   201914/06

88 • Position paper on terminology in Pharmacogenetics - EMEA/CPMP/3070/01

89 • Rules governing medicinal products in the European Union Volume 2C Notice to applicants; A
90   guideline on summary of product characteristics (SmPC) September 2009

91 • Note for Guidance on definitions for genomic biomarkers, pharmacogenomics, pharmacogenetics,
92   genomic data and sample coding categories - EMEA/CHMP/ICH/437986/2006 (ICH Topic E15.).

93 • Note for Guidance on genomic biomarkers related to drug response: context, structure and format
94   of qualification submissions - EMEA/CHMP/ICH/380636/2009 (ICH Topic E16).

95 • Guidelines on good pharmacovigilance practices (GVP):
96   - Module V – Risk Management Systems
97   - Module VI - Management and reporting of adverse reactions to medicinal products
98   - Module VII – Periodic safety update report
99   - Module VIII- Post-authorisation safety studies
100   - Module IX – Signal management
101   - Module XVI - Risk minimisation measures: selection of tools and effectiveness indicators

102 • Post-authorisation efficacy studies (PAES) when finalised.

103 4. Special characteristics of pharmacogenomics in
104 pharmacovigilance

105 *4.1. Types of genomic biomarkers*

106 4.1.1. Biomarkers (BM) related to Pharmacokinetics (PK) and/or
107 Pharmacodynamics (PD)

108 The analysis of biomarkers that influence the exposure levels of drug or metabolite(s), and thereby
109 relate to dose/concentration-dependent effects has the potential to increase the safety and efficacy of
110 drugs during therapy. The role of drug metabolizing enzymes and transporter proteins relevant for
111 each drug from uptake to final elimination are expected to have been elucidated prior to approval of a
112 new medicinal product. The same is expected for polymorphic ADME enzymes and the genomic
113 variations that influence drug-drug interactions. In this respect, guidance on when and how to consider
114 pharmacogenetic/pharmacogenomic studies in drug development is provided in the relevant guidelines
115 "Guideline on the use of pharmacogenetic methodologies in the pharmacokinetic evaluation of
116 medicinal products - EMA/CHMP/37646/2009' and "Guideline on the Investigation of Drug Interactions
117 CPMP/EWP/560/95/Rev. 1".

118 However, depending on the state of the art knowledge at the time of drug development, only parts of
119 the data might be available pre-authorisation and further investigation or studies might be necessary
120 years after approval of the product. The clinical phenotype clues and

Guideline on key aspects for the use of pharmacogenomic methodologies in the
pharmacovigilance evaluation of medicinal products
EMA/281371/2013   Page 4/18

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

123 As an example of post marketing identification of a PK genomic biomarker with clinical impact on
124 benefit risk of a medicine, the case of CYP2C19 and the use of clopidogrel is presented below.

125 Clopidogrel, a prodrug used for prevention of athero-thrombotic events in coronary artery and
126 cerebrovascular disease or after stent implantation, is metabolised mainly by CYP2C19 to produce the
127 active metabolite that inhibits platelet aggregation (Mega et al. 2009). In patients who are CYP2C19
128 poor metabolisers, less of the active metabolite is formed, which may result in serious clinical
129 implications (e.g. stent thrombosis, myocardial infarction or even death). At the time of approval, it
130 was not possible to determine the active metabolites.

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

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

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

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

145 Warfarin, a vitamin K antagonist that inhibits the C1 subunit of VKORC1 enzyme complex, has a well-
146 known safety and efficacy profile. Certain single nucleotide polymorphisms (SNPs) in the VKORC1 gene
147 have been associated with variable warfarin dose requirements. Thus, different variants of VKORC1
148 sensitise individuals to warfarin are known, whereas disrupting mutations in VKORC1 may cause
149 warfarin resistance. Emerging data indicating also interethnic differences in such effect exist.

150 In addition to the variation in VKORC1 gene that affects the pharmacodynamics of warfarin, genetic
151 polymorphisms in CYP2C9 also affect PK of this drug. The variant alleles, *CYP2C9*2* and *CYP2C9*3*,
152 result in decreased clearance and higher blood level of S-warfarin, the more potent enantiomer,
153 increasing the risk of bleeding. Genotyping for these alleles has been shown to shorten the time to
154 reach the required therapeutic anticoagulation state (INR, international normalized ratio) (Pirmohamed
155 et al. 2013).

156 Thus, VKORC1 and CYP2C9 gene variants, together with known non-genetic factors, can explain about
157 half of the observed variability in warfarin dose requirements. Genotype information, when available,
158 may thus assist in dose selection (Lenzini et al. 2010).

159 4.1.2. Genomic biomarkers associated with drug-induced toxicity risk
160 status (e.g. human leukocyte antigen (HLA) alleles):

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

Guideline on key aspects for the use of pharmacogenomic methodologies in the
pharmacovigilance evaluation of medicinal products
EMA/281371/2013   Page 5/18

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

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

176 Another example of genomic BM predictive of immune mediated serious adverse reaction is HLA-
177 B*1502 allele for which the non-carrier status may predict the absence of the most severe skin
178 reactions induced by carbamazepine. In this case the NPV is of high clinical significance although the
179 PPV is low (see Annex 2). A strong association was noted between the absence of *HLA-B*15*02 and low
180 incidence of Steven Johnson syndrome (SJS) or other cutaneous reactions in retrospective post-
181 authorisation case-control studies. It is noted that the test for *HLA-B*1502* is most useful in certain
182 Asian populations (e.g. Han Chinese and Thai patients) due to high NPV as well as a relatively high
183 frequency of this allele in these populations. Clinical utility and effectiveness of the relevant risk
184 minimisation measure (i.e. genotyping subjects prior to use and avoidance of carbamazepine in *HLA-*
185 *B*1502* carriers) could be shown in a well-designed prospective study (Chen et al. 2011). The
186 importance of ethnicity and genomic BM status is also discussed in the next section.

4.2. Special or vulnerable populations

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

4.2.1. Ethnicity

193 Ethnic groups may differ in the prevalence of genomic biomarkers, in dosing needs and in the
194 susceptibility to adverse reactions. However, it is not always feasible to gather information about these
195 sub-populations during clinical trials due to a multitude of limitations and sometimes restriction by
196 legislation. In such instances, reference to main genomic databases such as National Center for
197 Biotechnology Information (NCBI), PharmacoGenomic Knowledge Base (GKB) and pharmacogenomic
198 data collection in the post authorization phase have a potential to elucidate any association with
199 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

201 The consequences of impaired renal function may be different in genetically different subpopulations.
202 This applies, e.g., if renal excretion is of increased relative importance in the genetic sub-population.
203 One example would be in the case of codeine metabolism in CYP2D6 ultra-rapid metabolisers (UM),
204 who will form more active metabolite such as morphine and morphine-6-glucuronide. The latter is
205 eliminated through the kidney. Higher plasma concentration of this active metabolite may be expected
206 in CYP2D6 UM patients, with renal impairment and may thus experience opioid intoxication. If in

Guideline on key aspects for the use of pharmacogenomic methodologies in the
pharmacovigilance evaluation of medicinal products
EMA/281371/2013   Page 6/18

207 addition the patient is taking concomitant medications that inhibit the alternative elimination pathways,
208 the risk for adverse reactions may be further increased as a result of higher active substances
209 accumulated.

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

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

219 Therefore, if a significant impact of a genetic polymorphism on the PK of a drug substance and/or the
220 risk for adverse reactions has been established in adults, the potential consequences in the paediatric
221 population should be further considered.

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

225 <u>Older patients</u>

226 Special considerations should be given to the impact of genetic polymorphisms on adverse reactions in
227 older patients, often resulting from drug-drug interactions in view of poly-medication, multiple
228 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)

234 The purpose of the safety specification in the RMP is to provide a synopsis of the safety profile of the
235 medicinal product(s) in the intended population as described in the approved Summary of Products
236 Characteristics (e.g. therapeutic indications, or contraindications), and should include what is known
237 and areas of uncertainty about the medicinal product(s).

238 Generally, it is expected to have data regarding relevant genomic BMs relating to efficacy or safety of a
239 new medicinal product, including patient selection or dose specification for genomic sub-populations,
240 available at time of marketing authorisation.

241 In the safety specification of RMP, important identified or potential risks or missing information related
242 to the use of the medicinal products in the target population and potential off-label use, should be
243 discussed with reference to pharmacogenomics. The aspects indicated below should be considered.

244 • Genomic sub-populations

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

Guideline on key aspects for the use of pharmacogenomic methodologies in the
pharmacovigilance evaluation of medicinal products
EMA/281371/2013   Page 7/18

247 In case the entire development programme has been conducted in subjects or patients with well
248 identified specific genomic variations, the ability to extrapolate the findings (efficacy and safety) to the
249 general population or subjects with different genotype will need to be discussed both within the pre-
250 authorisation dossier and in the RMP including appropriate pharmacovigilance activities and/or specific
251 risk minimisation measures. The discussion on important risks and missing information should include
252 the potential impact of the medicine in the extended populations and potential for off label use.

253 If a potentially clinically important genomic polymorphism has been identified but not fully studied in
254 the clinical development program, this should be considered as missing information or a potential risk
255 in the sub-populations.

256 This should be reflected in the safety specification.

257 • Patients of different ethnic origins

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

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

267 5.1.2. Pharmacovigilance plan (routine or additional activities)

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

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

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

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

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

Guideline on key aspects for the use of pharmacogenomic methodologies in the
pharmacovigilance evaluation of medicinal products
EMA/281371/2013   Page 8/18

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

Guideline on key aspects for the use of pharmacogenomic methodologies in the
pharmacovigilance evaluation of medicinal products
EMA/281371/2013
Page 9/18

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

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

336 Various clinical and epidemiological study designs and methods are used to assess the possible
337 association between drug induced ADRs and genomic BMs (see the following link:
338 http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_00041
339 1.jsp&mid=WC0b01ac058002958e).

340

341 In case of serious ADRs or lack of efficacy, the collection and storage of genomic material (e.g.
342 blood, saliva, and tissue) may prove essential to elucidate the potential importance of genomic
343 BMs (see the following link:
344 http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC50000
345 3864.pdf).

346 The following activities should be considered:

347 • Pharmacogenomic surveillance system: genomic biological samples should be collected prior to
348 prescription of medicines for which the therapeutic indication and contraindication is determined by
349 genomic BM, and when, because of narrow therapeutic index, dosing is adjusted by genomic BM.

350 • In addition, from every patient receiving a medication and experiencing serious ADRs or lack of
351 effectiveness, it should be encouraged that genomic samples be collected especially in the initial
352 post-authorisation period so that e.g. DNA traits from such patients could be compared with those
353 of patients without those safety or efficacy concerns. On a case by case basis genomic material
354 sampling might be part of product-specific RMP.

355 • Collaborative actions, such as a consortium (biobanking)-based approach involving MAHs,
356 academia and regulatory authorities should be considered.

357 • To map pharmacogenomic risk factors for drug responses it is recommended to incorporate
358 genomic data into databases with individual clinical phenotype. Collecting genomic BM information
359 from academic pharmacoepidemiological networks databases may be explored as appropriate.

360 • Internationally recognized pharmacogenetic/pharmacogenomic terms (including those that are
361 included in MedDRA) should be used for data mining or data presentation, as appropriate.

362 • 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

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

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

Guideline on key aspects for the use of pharmacogenomic methodologies in the
pharmacovigilance evaluation of medicinal products
EMA/281371/2013   Page 10/18

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

371 The evaluation of data may relate to the strength of an association between a genomic BM, measured
372 with a validated test method, and a safety concern, to severity/magnitude of the effect, and to patient
373 ethnicity. To be noted here is the consideration that while PPV is important for efficacy biomarkers, the
374 NPV more commonly is important for the safety biomarkers (for the avoidance or minimisation of
375 safety risks).

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

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

384 For the evaluation of genomic BM related to PK (e.g. polymorphisms in drug metabolising enzymes,
385 such as CYP2D6, or transporters such as SLCO1B1) or PD, the clinical variables may include level of
386 drug concentrations, in addition to lack of efficacy or particular toxicity. The potential differences
387 regarding the PK/PD related clinical variables and genomic BM in different ethnic populations should be
388 considered as appropriate. When evaluating the predictive value of the genomic BM, the sensitivity and
389 specificity of the testing should be presented.

390 It should also be considered that the phenotype cannot always be predicted from a genotyping test
391 especially in the context of polymorphic metabolising enzymes and transporters because of e.g. food or
392 concomitant medications. Therefore as relevant measuring metabolic phenotype (e.g. plasma
393 concentration of the drug and/or metabolites) should be considered. Effects related to gene copy
394 number should be considered. In clinically relevant and well defined cases the genomic BM may help
395 optimal dosing.

396 Regarding the evaluation of data sources and level of certainty on the evidence, the types of studies,
397 methodology adopted and consistency of the results should be considered. For recommendations on
398 genomic testing, the presence or absence of therapeutic alternatives should be considered. The risk
399 increase in patients with the genomic BM should be presented in relative as well as absolute terms.

400 ## 5.3.2. Level of evidence

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

403 Clinical validity refers to the accuracy with which a test detects or predicts a given phenotype (clinical
404 disorder or outcome). Clinical utility refers to the net balance of risks and benefits associated with
405 using a test in routine practice, including its ability to inform clinical decision making, prevent adverse
406 health outcomes (e.g. morbidity, mortality), and predict outcomes considered important to patients
407 and their families.

408 In general, the ACCE model process (analytic validity, clinical validity, clinical utility and associated
409 ethical, legal and social implications) that includes collecting, evaluating, interpreting, and reporting
410 data about genetic testing, should be considered (CDC: ACCE Model Process for Evaluating Genetic
411 Tests).

Guideline on key aspects for the use of pharmacogenomic methodologies in the
pharmacovigilance evaluation of medicinal products
EMA/281371/2013   Page 11/18

412 Information relating to genomic BMs and their potential effect on drug therapy may arise late in drug
413 development when a number of clinical trials are completed or post authorisation. When such
414 retrospective evidence is gathered or presented, there are certain caveats/requisites for its evaluation:
415 ideally data should be derived from well conducted randomised clinical trials, where the genomic BM
416 status and the clinical information are available from the majority of the subjects and represent the
417 population of interest (to avoid selection bias), and the retrospective analysis should be pre-planned.
418 In the post authorisation phase, when signals are identified, replication of the association from
419 different datasets adds significant value. Isolated retrospective observations are expected to provide
420 confirmatory evidence whenever clinically and ethically appropriate.

421 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

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

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

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

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

5.3.4. Effectiveness of the risk minimisation measures

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

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

Guideline on key aspects for the use of pharmacogenomic methodologies in the
pharmacovigilance evaluation of medicinal products
EMA/281371/2013   Page 12/18

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

457 One example of a study evaluating the effectiveness of risk minimisation measures is the study on
458 *HLA-B*1502* allele screening before starting carbamazepine treatment in Han Chinese. It was shown
459 that identification of *HLA-B*1502* carriers and avoidance of carbamazepine in these subjects was
460 strongly associated with a decrease in the incidence of carbamazepine induced SJS – Toxic epidermal
461 necrolysis (TEN) (Chen et al. 2011).

462 Definitions and abbreviations

463 Definitions

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

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

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

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

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

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

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

481 Pharmacovigilance (PhV): the science and activities relating to the detection, assessment,
482 understanding and prevention of adverse effects or any other drug-related problem. The aims of PhV
483 are to enhance patient care and patient safety in relation to the use of medicines; and to support
484 public health programmes by providing reliable, balanced information for the effective assessment of
485 the risk-benefit profile of medicines (WHO).

486 Abbreviations

487 ADME: absorption, distribution, metabolism, and excretion

488 BM: biomarker

489 DNA: Deoxyribo Nucleic Acid

490 GVP: Good Pharmacovigilance Practice

491 NPV: Negative Predictive Value

492 PAES: post authorization efficacy studies

493 PASS: post authorization safety studies

Guideline on key aspects for the use of pharmacogenomic methodologies in the
pharmacovigilance evaluation of medicinal products
EMA/281371/2013   Page 13/18

494 PD: pharmacodynamics

495 PI: product information

496 PK: pharmacokinetics

497 PM: poor metaboliser

498 PPV: Positive predictive value

499 PSUR: Periodic safety update report

500 RMP: Risk Management Plan

501 RNA: ribonucleic acid

502 SJS: Stevens–Johnson syndrome

503 SNP: Single Nucleotide Polymorphism

504 SmPC: summary of product characteristics

505 TEN: Toxic epidermal necrolysis

506 UM: ultra-rapid metaboliser

507 VKOR: vitamin K epoxide reductase

References

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

511 Chen P, et al. Carbamazepine-Induced Toxic Effects and *HLA-B*1502* Screening in Taiwan. N Engl J
512 Med. 2011;364:1126-33.

513 EMA home page with lists of scientific guidance documents on pharmacogenomics:
514 http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000411.js
515 p&mid=WC0b01ac058002958e

516 EMA home page – Reflection paper on pharmacogenomic samples, testing and data handling:
517 http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC50000386
518 4.pdf

519 Lenzini P, et al. Integration of genetics, clinical, and INR data to refine warfarin dosing. Clin Pharmacol
520 Ther. 2010; 87: 572-578.

521 Mallal S, et al. *HLA-B*5701* screening for hypersensitivity to abacavir. N Engl J Med. 2008;358:568-79.

522 Mega JL, et al. Cytochrome p-450 polymorphisms and response to clopidogrel. N Engl J Med.
523 2009;360:354-62.

524 Pirmohamed M, et al. A Randomized Trial of Genotype-Guided Dosing of Warfarin. N Engl J Med. 2013;
525 Nov 19. [Epub ahead of print].

Annexes

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

Guideline on key aspects for the use of pharmacogenomic methodologies in the
pharmacovigilance evaluation of medicinal products
EMA/281371/2013   Page 14/18

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

531 Section 4.2: "Special populations: patients with a particular genotype where dose is different in special
532 populations or use is different with cross-reference to other relevant sections for further detail as
533 appropriate."

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

536 Section 4.4: Subjects with a specific genotype or phenotype might either not respond to the treatment
537 or be at risk of a pronounced pharmacodynamic effect or adverse reaction. This should be described as
538 warnings or precautions.

539 Section 4.5: "Additional information on special populations. If there are patient groups in which the
540 impact of an interaction is more severe, or the magnitude of an interaction is expected to be larger
541 e.g. patients with decreased renal function (in case the parallel pathway is renal excretion), paediatric
542 patients, elderly etc., this information should be given here."

543 Section 4.8: "e. <Other special populations> This section may include information on any clinically
544 relevant differences (i.e. in nature, frequency, seriousness or reversibility of adverse reactions, or need
545 for monitoring) specifically observed in other special populations such as elderly, patients with renal
546 impairment, patients with hepatic impairment, patients with other diseases or a specific genotype.
547 Cross-reference to other sections such as 4.3, 4.4 or 4.5 may be added as appropriate."

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

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

552 Section 5.2: Variations with respect to polymorphic metabolism should be described, if clinically
553 relevant, in quantitative terms (with cross-reference to 4.2 when applicable). The frequencies of the
554 alleles of interest affecting pharmacokinetics in ethnic populations should be presented.

Guideline on key aspects for the use of pharmacogenomic methodologies in the
pharmacovigilance evaluation of medicinal products
EMA/281371/2013   Page 15/18

555 Annex 2. <u>Examples – from data evaluation to labeling</u>

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

556