24 September 2015
EMA/CHMP/610677/2015
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Guideline on key aspects for the use of pharmacogenomic methodologies in the pharmacovigilance evaluation of medicinal products' (EMA/CHMP/281371/2013)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	IFAPP (International Federation of Associations of Pharmaceutical Physicians)
2	CBG-MEB
3	European Research Network Pharmacogenetics/genomics
4	GSK
5	ESPT (European Society for Pharmacogenetics and Theranostics)
6	Agency for Medicinal Products and Medicinal Devices of Croatia (Halmed)
7	F.Hoffmann – la Roche Ltd.
8	EBE (European Biopharmaceutical Enterprises)

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	We agree on the content of this guideline.	
2	The MEB welcomes the present concept guideline on the use of pharmacogenomic methodologies in the post-approval setting, and acknowledges the opportunity of pharmacovigilance pharmacogenomic evaluations in explaining differences in treatment response. In general, it is considered that the concept guideline describes the key considerations and challenges with regard to the establishment of a pharmacogenomic pharmacovigilance program. We support the present concept guideline, and believe it provides a good basis for further discussion. We would like to add the following general and specific (see below) considerations: - The scope of the current guideline is limited to *genomic* biomarkers, while other types of biomarkers (e.g. phenotypic biomarkers, tumour specific markers such as HER2 status in breast cancer) have also shown to be important predictors of interindividual variability in treatment response. Please consider to refer to further relevant guidelines on other types of biomarkers, or to widen the scope of the present guideline. - Pharmacovigilance planning is considered particularly important to ensure a solid methodological approach in evaluating (potential) pharmacogenomic biomarkers, including the use of clinically relevant endpoints and to guarantee sufficient study power. The proposal to evaluate (potential) biomarkers through	1. Please consider to refer to further relevant guidelines on other types of biomarkers (phenotypic biomarkers, tumour specific markers), or to widen the scope of the present guideline. Comment: Regarding tumour specific markers, “Guideline on the evaluation of **anticancer medicinal** products in man” (dated 13 December 2012, EMA/CHMP/205/95/Rev.4, by Oncology Working Party) **can be referred** to, where “Biomarkers” as a heading is included. 2. The proposal to evaluate (potential) biomarkers through RMP-based pharmacovigilance planning is hence supported. Comment: Acknowledged. 3. The term ‘clinical phenotype’ is considered an ambiguous term. Please consider to add a definition. Comment: Agreed, and also definitions of “phenotype” (and polymorphism) are given.

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	RMP-based pharmacovigilance planning is hence supported. - It was noted that throughout the concept guideline the term 'clinical phenotype' is used, which is considered an ambiguous term. Please consider to add a definition.	
3	The European Research Network on Pharmacogenetics/genomics encourages the writing of guidelines on the use of pharmacogenomics methodologies in the evaluation of medicinal products. We would like to emphasize that we agree with the authors of the draft guideline about the importance of setting up DNA banks for all clinical trials. The information that can be obtained from this will be pivotal in performing studies to make clinical implementation of PGx possible. Furthermore we think it is positive that the authors of the draft guideline emphasize the importance of the need to cover different ethnicities and different age groups. However, we also have some concerns regarding the guidelines as they are written at the moment. Firstly, the document is very much written as a summary of successes in pharmacogenetics/genomics (PGx). Important current examples including some relating directly to implementation of testing are reviewed. However, it is not clear that these will be relevant to new medicines. Pharmacogenomics generally, particularly the genetics of drug efficacy and susceptibility to adverse drug reactions (ADRs), is a complex subject, which is likely to involve more than the mentioned single SNP-drug interactions.	1. The document is very much written as a summary of successes in PGx. However, it is not clear that these will be relevant to new medicines. PGx, is a complex subject, which is likely to involve more than the mentioned single SNP-drug interactions. Comment: Efforts have been made to focus on providing as clear guideline as possible in sections 5.1 and 5.2.
3	As we mentioned before in the document it is indicated that it is important to assess the frequencies in different ethnic populations. Indeed this is important but it is not always the case that common	1. Ethnicity: It is important to assess the frequencies in different ethnic populations. It is mentioned that the phenotype cannot always be determined based on the

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	variants in a gene explain the phenotype. At the same time it is mentioned that the phenotype cannot always be determined based on the genotype but e.g. based on food or concomitant medications. However it might also be explained by the presence of rare variants in the gene of interest. Individually the frequency is low but all together these might explain a larger proportion of the patients that show lack of efficacy or side effects than common variants alone. This might be especially important seen the developments in genetics were more and more whole exome/genome sequencing is applied. The document is limited to the germ line genome and does not consider other genomes that may be present in an individual (i.e. tumor genome, bacteria etc) that may affect drug response. The document appears to be limited to SNPs while other genomic variants may also be important (i.e. copy number variants, mutation, tandem repeats etc.) The guidelines part of the document is still vague. It is not clear what needs to happen in the relation to new drugs. The main actions described are for gene-drug interactions that are already known. And even for those interactions action to be taken is vague. The manufacturer should show by literature review or by investigation that known polymorphic enzymes, such as CYP2D6, CYP2C9 and CYP2C19 are not interfering.	genotype but e.g. based on food or concomitant medications. However it might also be explained by the presence of rare variants in the gene of interest. Comment: Agreed. The point is clarified by adding **rare variants** in the gene in ethnic groups. 2. The document is limited to the germ line genome and does not consider other genomes that may be present in an individual (i.e. tumor genome, bacteria etc) that may affect drug response. Comment: See above 2.1. 3. The document appears to be limited to SNPs while other genomic variants may also be important (i.e. copy number variants, mutation, tandem repeats etc.) Comment: Copy number of genes is mentioned. 4. The guidelines part of the document is still vague. It is not clear what needs to happen in relation to new drugs. Even for interactions action to be taken is vague. The manufacturer should show by literature review or by investigation that known polymorphic enzymes, such as CYP2D6, CYP2C9 and CYP2C19 are not interfering. Comment: The Draft Guideline section 5.1 outlines the Risk Management Plan (RMP) which provided what is expected from the manufacturer. However, the suggested improvement has been taken into account.

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3	However there is no guidance on how to discover which gene-drug interactions might be of importance for a new drug. We suggest that for each new drug being developed, an individual PGx plan is needed. The contents of this plan will vary by drug and can be informed by results from pre-clinical studies on the contribution of metabolic enzymes including the cytochromes P450 and drug transporters to disposition of the drug, and what is known about the drug target with provision also for more open analyses such as genome-wide association studies which are likely to be especially relevant to idiosyncratic toxicities. This PGx plan should be in place before the start of phase III and continue into the pharmacovigilance phase. To be able to perform these pharmacovigilance analyses in a comprehensive manner, informed consent for a range of genetic analyses from genotyping to single SNPs to whole genome sequencing should be obtained for the banked DNA samples at the time they are collected. Another concern that we have is the communication of gene-drug interactions to patients and physicians. The body of evidence needed before these interactions are included in the patient information sheet should be well defined. Furthermore the positive predictive value should be sufficiently high. The possibility that patients may be uncertain about their medication use because of unclear information about PGx in the patient leaflet should be avoided. If specific advice on genotyping for a pharmacogenomic biomarker appears in the leaflet, it is important that an appropriate genetic test should be available to the patient and prescriber. This is already feasible for some well-established markers (for example HLA B*57:01 for those to be prescribed abacavir) but for other genes/alleles mentioned, this may be more problematic. For example, the document mentions	5. There is no guidance on how to discover which gene-drug interactions might be of importance for a new drug. It is suggested that for each new drug being developed, an individual PGx plan is needed. Comment: While the idea of an individual PGx plan may be relevant, it is not considered warranted as the GVP module V on RMP includes elements of PGx information for all products. With regards to the earlier phase (before phase III studies) drug development, guidance may be found in other relevant EMA guidance documents (PK/PGx; PGx methodology issues; etc). However, our draft guideline sections 5.1 and 5.2 may be modified for clarity. 6. Another concern is the communication of gene-drug interactions to patients and physicians. Comment: The comments on the body of evidence needed before gene-drug interactions are included in the PIL should be well defined; the PPV should be sufficiently high; avoid unclear message; genetic test should be available if advice for genetyping is given; are acknowledged. Section 5.3.3 of the guideline has been amended to reflect some of these aspects.

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	CYP2D6 ultrarapid metabolizers (UM). It is unclear whether any currently available genotyping or phenotyping approaches are adequate for detection of all such individuals. If EMA finds a test important, it can go in the advisory part in the label with the intent to make it more stringent later on, so move it after (a standard of 1-2 years) into a more obligatory part of the label (if it needs to be there), so that laboratories and industry have the opportunity to develop an appropriate test. The European Research Network on Pharmacogenetics/genomics is willing to contribute to the writing of a second draft of this guideline.	
4	GSK welcomes the opportunity to comment on this draft guideline. We believe this guideline will be useful to sponsors who conduct pharmacogenomic research on medicinal products.	Comment: none.
5	The European Society for Pharmacogenetics and Theranostics (ESPT) greatly values the EMA initiative for generation of guidelines on pharmacogenomics methodologies and pharmacovigilance, and very much appreciate the current draft guideline. The draft guideline provides an excellent overview and a summary of important examples. However, to our feeling, the specific recommendations of this manuscript are not very visible: specific issues on what should actually be done, and how this could it be implemented would benefit in our view from a summarizing paragraph with the specific recommendations of this guideline. As for the consideration of different aspects for evaluating safety genomic BM (line 376), it is not clear how the outcome of these aspects should be taken into account. As a suggestion, one could define weighing the evidence according to standard measures (e.g.	1. The specific recommendations of this manuscript are not very visible: specific issues on what should actually be done, and how this could be implemented would benefit from a summarizing paragraph with the specific recommendations of this guideline. Comment: The draft guideline follows the EMA Guideline template. However, a summarising remark has been considered as relevant. 2. As for the consideration of different aspects for evaluating safety genomic BM, it is not clear **how** the outcome of these aspects should be taken into account. Comment: The suggestion “to define weighing the evidence

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	randomized controlled trials, versus good clinical retrospective studies versus less well defined retrospective studies versus case reports) and the implications (e.g. effects on PK, effects on PD, with subdivision into minor effects, severe side effects or risk of death). In this way, we feel that the considered aspects can be weighed and quantified better. ESPT is willing to further help in finalizing this guideline, if felt needed.	according to standard measures (e.g. randomized controlled trials, versus good clinical retrospective studies versus less well defined retrospective studies versus case reports) and the implications (e.g. effects on PK, effects on PD, with subdivision into minor effects, severe side effects or risk of death)", is acknowledged and sections 5.3.1 and 5.3.2 have been amended.
6	According to recent studies, genomic biomarkers 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 into the significance of genomic biomarkers in 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.	1. Genomic biomarkers seem to be of special relevance for the patients on polypharmacy. This includes both testing for polymorphic metabolic enzymes and drug transporters with the influence on drug disposition in patients using interacting medicines. Comments: The suggestion on encouraging further investigations into the significance of genomic biomarkers in reduction of safety risks in patients taking multiple medicines, is acknowledged. However, this aspect is covered in **other 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". Nevertheless, the section **4.2 has been amended** to reflect this point.
7	The topics outlined in the guideline **concept statement** have been **addressed loosely** in the draft guideline and the draft guidance attempts to provide multiple **examples** for most topics. While this can be useful, it also **dilutes** clarity on the guidance being given. The guidance should be consolidated and may require some restructuring	Comments: The suggestion that the guidance should be consolidated and may require some restructuring of content, is acknowledged.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	of content.	
8	EBE welcomes the opportunity to provide feedback on the draft guideline on key aspects for the use of pharmacogenomic methodologies in the pharmacovigilance evaluation of medicinal products (EMA/281371/2013) and appreciate the regulatory need for this guideline.	
8	There are significant concerns about collecting genetic samples for spontaneous adverse events in the post-authorization environment. The proposed **guideline focuses on the responsibilities of the marketing authorization holder (MAH)**. However, the MAH does not always interact directly with those conducting post-authorization studies. It is therefore suggested that consideration be given to widening the scope of the guideline to **cover the diagnostics industry, and the professional societies** representing those who monitor/perform diagnostic testing in clinical practice. The monitoring of genomic testing may be **best achieved through professional societies' quality assurance program**, rather than through a risk management plan (RMP). **Challenges and potential barriers for collecting samples and other relevant data in a post-marketing setting** include: • For genetic samples, the lack of quality control, sampling consistency, storage conditions, evaluation methods, etc. • The absence of control samples from comparable sources and low acquisition rate, leading to bias in interpretation • The impact on patients (e.g. convenience, time, cost, lack of third-party reimbursement)	1. Concerns on genetic samples for spontaneous AEs. Comments: The concerns are acknowledged. However, section 5.2 (line 355-356) did mention "Collaborative actions, such as a consortium (biobanking)-based approach involving MAHs, academia and regulatory authorities…". Nevertheless, **diagnostics industry, and the professional societies** are now mentioned. 2. Challenges and potential barriers for collecting samples and other relevant data in a post-marketing setting Comments: The challenges are acknowledged. Section 5.2 has been amended.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	• The ethical and legal implications on patients' right to privacy • The impact on prescribers, e.g. will physicians choose a therapeutically less desirable drug for a patient in order to avoid sampling? • The absence of standardized logistics to secure patient and health professional cooperation and for compensating them for additional activities and services. There are also concerns about the analysis of samples that are obtained from a variety of sources. • Technology is constantly evolving and samples may be genotyped using different platforms • Sources of genomic information will need to be carefully evaluated prior to being included or combined in a study Proposed change (if any): The factors listed above **should be acknowledged in the guideline**. If the intent is to promote collection of biomarker data outside the purview of controlled clinical studies, the guideline should **discuss theoretical and actual circumstances** under which it should be done and **how** this data should be analysed (e.g. through collaborative research initiatives such as the SAE consortium).	
8	A significant issue for multi-national companies is the development of standards that are not consistent across regulatory territories. National or regional requirements that conflict with internationally-accepted standards are inefficient, duplicative, costly, and can detract from the discovery and development of new therapies. We recognize that regulations and **standards for pharmacogenomics-**	3. Encourage the EMA to **liaise** with health authorities outside Europe and determine if the spirit of its proposed guideline is in harmony with those that may be under development by other agencies. Comments: Acknowledged.

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	related pharmacovigilance are in early stages. However, we encourage the EMA to **liaise** with health authorities outside Europe and determine if the spirit of its proposed guideline is in harmony with those that may be under development by other agencies.	
8	Pharmacogenomics testing impacts the patient. While the draft guideline explains how the information can be included in the Summary of Product Characteristics (SPC), it does not give any guidance on **how this information can be reflected in a patient friendly manner in the Package Leaflet**. Proposed change (if any): Include text for the package leaflet in the final guideline.	4. Include text for the package leaflet in the final guideline. Comments: Acknowledged, but not considered needed.
8	The title implies that the guideline is for pharmacogenomic methodologies, however the guideline refers to and provides examples for variations in DNA but not RNA. Proposed change (if any): The title of the guideline should be changed from ~~pharmacogenomic~~ to **pharmacogenetic** and the scope section of the guideline (Section 2) should include a sentence stating that "**RNA markers are not discussed in this guideline**." Alternatively, the guideline could provide examples of RNA characteristics as related to drug response.	The guideline refers to and provides examples for variations in DNA but not RNA. Comments: The suggestion to change the title of the guideline from ~~pharmacogenomic~~ to **pharmacogenetic** and the scope section of the guideline (Section 2) should include a sentence stating that "**RNA markers are not discussed in this guideline**.", is acknowledged, but not accepted.
8	The guideline interchanges the terms pharmacogenomics and pharmacogenetics, and uses different punctuation for benefit/risk (e.g. benefit/risk, benefit:risk).	5. Comments: **Benefit / risk is used in the text**.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
110-114	8	Comments: Although ADME for a molecule is studied extensively during drug development, the knowledge at the time of drug development may not be fully elucidated, and at this time the science has not evolved such that every approved medicinal product will have data available pre-authorisation. Proposed change (if any): “The role of drug metabolising enzymes and transporter proteins most relevant for each drug from uptake to final elimination are ~~expected to have been~~ recommended to be elucidated prior to approval of a new medicinal product. The same is expected for the more common polymorphic ADME enzymes and the genomic variations that influence drug-drug interactions”.	Accepted.
123-186	7	Comments: The examples given of PK-, PD- or immune-mediating genomic biomarkers are helpful. However, the details on the examples could be **reduced** to consolidate the message.	Accepted.
138-139	8	Comments: The guideline could provide additional information about the studies examining the effect of CYP2C19 inhibitors on clopidogrel exposure and their impact. Proposed change (if any): “Similar effects on safety have been postulated to occur when clopidogrel was used with CYP2C19 inhibitors (e.g. proton pump inhibitors). In a crossover clinical study, clopidogrel exposure was decreased when clopidogrel and omeprazole (protein pump inhibitor) were co-administered. The product information for clopidogrel (Interaction with other medicinal products and other forms of interaction) was updated.	The proposed change is not acceptable. There are comments suggesting the example part should be shorter.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
145-158	8	Comments: The guideline could provide information on impact of VKORC1 and CYP2C9 variants on warfarin dosing decisions, and the interethnic differences for variable warfarin dose requirements. Also, it would be helpful to include a sentence describing the relationship between VKORC1 polymorphisms and the resulting PD effect on the subjects. Proposed change (if any): Add the following sentences: "post-authorisation studies provided evidence to include VKORC1 and CYP2C9 variants in the dosage and administration and clinical pharmacology sections of the drug label" (following line 158). "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.~~ Patients with certain sensitizing VKORC1 variants (e.g. 1639A at res992323) require a lower warfarin dose (mean dose 24-26 mg/week) compared to wild-type carriers (35 mg/week). Likewise, certain genetic variants in VKORC1 (e.g. 9041A at rs7294) are associated with the requirement for higher warfarin dose (mean dose 40 mg/week). Emerging data indicate~~ing also~~ interethnic differences ~~in such effect~~ exists; for example, the allele frequency for a VKORC1 promoter polymorphism associated with warfarin sensitivity is greater in Asians than Caucasians."	The text is amended.
156-158	8	Comments: As model-based approaches are now scientifically accepted and are used to understand impact of multiple extrinsic and intrinsic factors on PK/safety issues (warfarin example used model-based approaches), we believe this guideline should indicate that the marketing authorisation applicant/holder could use these model-	Not accepted. PBPK seems more important in drug development than in PhV.

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		based approaches. Proposed change (if any): Add a sentence(s) to the guideline (in an appropriate location) commenting on the possibility of when/how to use model-based approaches. "**For example, physiologically based pharmacokinetic (PBPK) models may be constructed starting at early phase clinical trials, which incorporate both drug-dependent and independent variables to predict impact of various factors on PK variability and associated potential safety concerns." (Eissing T et al., Mol Diagn Ther 2012; 16(1)43-53)**.	
158	4	Proposed change (if any): It may be more appropriate to state "...may thus assist in initial dose selection." Doses are subsequently individualised based on INR.	Accepted.
161-162	8	Comments: The guideline could define "risk status" in the following sentence, "Serious reactions not dependent on the level of drug exposure (PK) or drug action (PD) may relate to patient risk status." The meaning of risk status is not clear. Proposed change (if any): "Serious reactions not dependent on the level of drug exposure (PK) or drug action (PD) may relate to **genomic variations that could increase the patients risk ~~status~~ to develop an adverse event**."	Accepted.
167	8	Comments: The guideline could expand the description of abacavir. Proposed change (if any): 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 analog reverse transcriptase inhibitor** (Mallal et al 2008).	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
180	4	Comments: typographic error. Proposed change (if any): Steven**s** Johnson syndrome.	Accepted.
181-183	8	Comments: The guideline could provide additional information around allele frequency required for screening prior to drug administration. For example, the guideline suggested that HLA-B*1502 should be screened in certain Asian populations, even though the risk allele is found in very low frequency in other populations. A statement should be included on why other Asian populations and non-Asian populations are not screened. Proposed change (if any): "**Certain Asian populations and non-Asian populations are not screened for HLA-B*1502 as the allele frequency for the risk allele is <1% in these populations. Screening risk alleles with low minor allele frequencies may not be feasible**".	The text is amended.
188-189	8	Comments: The factors listed in the following sentence tend to be related to personal traits. We suggest the wording below to be more consistent. Proposed change (if any): "Optimal drugs and drug doses for individuals may depend on a number of factors such as gender, age, body weight, ethnicity, genetic variation, co-morbidity, drug–drug interactions ~~pharmacogenomics~~."	Accepted.
197	4	Comments: incorrect acronym. Proposed change (if any): PharmacoGenomics Knowledge Base is PharmGKB.	Accepted.
197	5	Comments: the abbreviation for the PharmacoGenomic Knowledge	Accepted.

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		Database is not GKB. Proposed change (if any): **Change to PharmGKB.**	
199	4	Comments: If collection of PGx samples among some sub-populations is restricted by legislation during clinical trials (lines 195-6), we suspect that these same restrictions may exist in post-authorization surveillance so referenced genomic databases may not address this knowledge gap. Proposed change (if any): none proposed.	
200	7	Comments: Sub-section: *Impaired or immature organ function and age* – topics should be handled separately as each is an independent topic. Proposed change (if any): Separate topic to 4.2.2 *Impaired or immature organ function ~~and age.~~*	Accepted.
200-228 Section 4.2.2.	8	Comments: Create a new section for age. Also the guideline is not clear on whether a drug would be studied in a paediatric population if the drug is expected to be highly affected by CYP3A7, CYP2C9, 2C19 and 3A4. Proposed change (if any) : 4.2.3 *Elderly or Paediatric Populations*. "**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 and justifications for conducting a study in the paediatric population should be further considered.**"	The text is amended.
200-228 Section	8	Comments: The sub-section "Impaired or immature organ function and age" should be in different sub-sections as each is an	Not accepted. It is unclear if the hepatic function example reflects changes/importance

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4.2.2.		independent topic. Also, an impaired hepatic function example could be provided. Proposed change (if any): Separate topic to 4.2.2 *Impaired or immature organ function* ~~*and age*~~ **Hepatic function example**: "Drug dose adjustments may need to be made in patients with liver disease, or receiving concomitant drugs that inhibit metabolic enzymes. For example, patients with elevated bilirubin treated with irinotecan have an increased risk of toxicity and irinotecan dose reduction is recommended."	in genetic subpopulations.
222-224	8	Comments: It is not clear if it is suggested that a new study or a label update is required for opioid intoxication-triggered fatal outcome in breast fed children of mothers who are UMs. We suggest the following change. Proposed change (if any): Opioid intoxication including fatal outcome has been reported in breast fed children of mothers who are UMs. Therefore relevant information or lack of information regarding the importance of genomic factors for pregnancy and lactation **should be considered** in the labelling.	Not accepted. The referred example (codeine) has a labelling in EU SPC section 4.6. The proposed addition is not considered relevant here. However, "should be considered" is changed to "**has been included** in the labelling **for codeine**."
223	5	Comments: "…children of mothers who are UMs". UM was not specified in the text earlier. Further, it is important that it concerns CYP2D6 UMs (and not for instance CYP2C19 UMs) and that the UM status in the evidence provided was based on genotyping. Based on metabolic ratio, more individuals may be CYP2D6 UM, and this may indeed also be a risk, but according to our understanding, this has not been documented so far. **Proposed change** (if any): "…children of mothers that are CYP2D6 ultrarapid metabolizers (UMs), as identified based on the presence of	The text is amended.

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		a CYP2D6 gene duplication in the absence of CYP2D6 non-functional alleles".	
225	7	Comments: Guidance addressing *Older Patients* should be covered in a separate subsection. Proposed change (if any): **4.2.3** *Elderly Patients.*	"Geriatric populations" is used now.
238-240	7	Comments: At the time of marketing authorisation, information on the safety of a medicinal product is generally relatively limited and therefore so is the ability to assess genomic sub-populations for safety. Proposed change (if any): Generally, it is ~~expected~~ **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 sub-populations, available at time of marketing authorisation.	Accepted.
238-243	8	Comments: In the current state of the art, it appears overly ambitious to state that relevant biomarkers would be known at the time of market authorization. For example, post approval studies of >5,000-10,000 patients may be necessary to elucidate safety biomarkers. This represents far more subjects than would typically be included in the pivotal studies. Use of prospective randomized clinical trials for identification and validation of genomic BMs may be expensive and time and effort intensive. A retrospective analysis of several independent and completed RCTs, which may occur after medicinal products have been marketed, may be more feasible to validate genomic BMs. Proposed change (if any): "Generally, it is **desirable** ~~expected~~ to have data regarding relevant **and confirmed** genomic BMs relating	The text is amended.

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		to efficacy or safety of a new medicinal product, including patient selection or dose specification for genomic sub-populations, available at time of or after marketing authorization. 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 **when relevant data or evidence is available".**	
245-246	7	Comments: In addition to being genotypic, genomic polymorphism sub-populations may be due to age-related shifts. Proposed change (if any): The safety profile in such population, e.g. sub-population identified by a known and clinically relevant genomic BM, including known age-related genetic polymorphisms, should be discussed.	The effect of ontogeny of elderly is already mentioned in other part of the document.
247-248	8	Comments: The guideline does not provide rationale for developing a drug only in the genomic sub-population. We suggest adding the following statement to provide clarity. Proposed change (if any): "In case the entire development programme has been conducted in subjects or patients with well identified specific genomic variations (**for reasons that incremental benefit is likely to be only observed in the biomarker-positive sub-population)** the ability to extrapolate the findings…"	Accepted.
253-256	7	Comments: Include line 256 in prior paragraph to link concepts. Proposed change (if any): 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-p**opulations. This** should	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		be reflected in the safety specification.	
253-256	8	Comments: Include line 256 in prior paragraph to link concepts. Proposed change (if any): 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.	Accepted.
275	5	Comments: "When the genomic BM directly influences PD or efficacy (..) the relationship is likely to be characterized during the pre-authorization phase". This is an assumption, which, to our feeling, should not be in a guideline. **Proposed change** (if any): "When the genomic BM directly influences PD or efficacy (..) the relationship should be characterized during the pre-authorization phase, and the outcome of this should be taken up in the drug label."	The text is amended.
277-280	8	Comments: A biomarker may have reduced efficacy. We suggest changing lack of efficacy to reduced efficacy. It is not clear which population the MAH should develop their scientific rationale. We suggest modifying the sentence to describe the intended population. Proposed change (if any): However, in other cases a genomic BM may be an indicator of either ~~lack of~~ **reduced** efficacy or adverse reactions. It is important that the marketing authorisation applicant/holder has a strong scientific rationale behind the use of the product i**n the population for which use is intended** (e.g. both marker positive and marker negative subjects) and should keep focus on characterisation of the genomic BM impact on the safe use of the	The text is amended.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		product.	
278-280	7	Comments: Focus should remain on providing a rationale for the population for which product use is intended. Proposed change (if any): It is important that the marketing authorisation applicant/holder has a strong scientific rationale behind the use of the product in the population for which use is intended (e.g. 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.	The text is amended.
285-286	3	Comments: Additional text. Proposed change (if any): Identify special populations such as cancer, transplant recipients, geriatric patients etc., associated with specific treatments where genotyping should be performed before starting treatment.	The text is amended.
294	5	Comments: "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 metabolite) exposure. Alternatively, these patients may benefit from different dosing regimens". Avoiding the use of CYP2D6 substrates for the example of CYP2D6 is in our opinion too strong. Some drugs can be given at an alternative dose (which is indeed mentioned, but only later suggesting this is a last resort rather than the first logical step), or can be used in standard dose but with increased surveillance. To our feeling, this example thus too much points to non-use of drugs in general and should be rephrased. Proposed change (if any): **"In the case of genomic BM related to PK, e.g. CYP2D6, the implications for alternative dosing,**	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		increased surveillance or avoidance of particular drugs in patients with a variant genotype in order to prevent the ADRs related to increased drug (or metabolite) exposure”.	
294-296	8	Comments: The guideline was not clear on when/why to use different dosing regimens for PK biomarkers. We suggest combining two sentences. Proposed change (if any): In the case of genomic BMs related to PK, e.g. CYP2D6, avoid the use **or modify the dosing regimen** 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.~~	
297	8	Comments: The paragraph should follow the principles of GvP Module XVI regarding the additional risk minimisation measures. Proposed change (if any): “Depending upon the situation **and when routine risk minimisation measures are not sufficient additional risk minimisation measures**….”	Accepted.
301-362	7	Comments: Section 5.2 *Signal detection and genomic data collection*, seems an eclectic collection of topics, touching on pharmacogenetic influence on efficacy, ethics, potential genomics data sources, sampling, surveillance, joint collaborations, terminology etc. The **key guidance** should be drawn out and the section restructured.	The text is amended.
301-362 Section 5.2	8	Comments: As noted in the General Comments section, there can be significant ethical, logistical and legal barriers to collecting genetic samples from patients who have experienced serious adverse events or reduced efficacy. In our opinion it is not feasible or justifiable to collect, store, and evaluate genetic samples from the large volume of patients who may fall under these categories. Such programs should	The text is amended.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		be protocol-driven and should only be conducted where there is a clear scientific and medical precedent, and then only in the form of a controlled clinical study with clear objectives and timeframes. The guideline should provide additional information about these issues. Furthermore, at this time, the methods and sources listed to gather data on signal detection and genomic data collection are difficult to implement. ADR case reports: Currently genetic information is not typically collected in ADR case reports. Epidemiological studies: Often epidemiological studies are based on second-hand data sources e.g. claim data bases. Genomic samples/data has to be proactively collected. Proposed change (if any): Line 327: "Valuable information can be generated from well-documented case reports. **If genetic information was collected with the appropriate consent then** ~~including information on~~ the relationship between the genetic BM (genotype or phenotype) and the clinical feature of the adverse reactions **could be evaluated**. 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~~ **support** product information change and/or trigger pharmacogenetic research". Line 333: "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. **Sources of genomic information will need to**	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		be carefully evaluated prior to be included in meta-analyses."	
306	4	Comments: Prescribing information has included reference to CYP2C9, CYP2C19 and CYP2D6 for implicated medicines. It would be helpful if the guideline could provide example prescribing information where reference to drug **transporters** (PK and/or PD level) or **pharmacological targets** (specifically where reference to voltage-gated potassium channels related to congenital long QT syndromes) is made.	The effect of transporter BM SLCO1B1 is described shortly with the example of simvastatin.
313-314	8	Comments: At this time, it may be difficult to implement post-authorization studies to investigate the pharmacogenetic influence of therapy failure. Proposed change (if any): "In addition, pharmacogenetic influence on the occurrence of therapy failure ~~should~~ **could** be investigated in the post-authorisation period."	Accepted.
318	5	Comments: the paper indicates what COULD be done. Rather, we would expect to see in a recommendation paper the items which SHOULD be done. Proposed change (if any): **change "could" to "should"**.	The text is amended.
318-345 376-399	2	Comments: Please consider to include further recommendations/ considerations for the different data sources, like the use of clinically relevant endpoints and to guarantee sufficient study power.	The text is amended by including "the use of clinically relevant".
323-326	8	Comments: A recommendation is made to collect "genomic data" for drugs with a narrow therapeutic index. For consistency with other guideline text, please change text to genomic samples instead. Proposed change (if any): "Genetic testing of all subjects and patients participating in clinical trials is being increasingly considered, and in	The text is amended.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		defined circumstances e.g. drugs with narrow therapeutic index, unpredictable serious ADRs, genomic ~~data~~ **sample** collection is recommended also for post-authorisation studies."	
330-331	7	Comments: A correlation between a genetic polymorphism and a potential ADR is unlikely to be demonstrated by single ADR report given the number of variables involved. In the absence of confirmatory data, product information changes should generally not be introduced on the basis of single, even well-documented, ADR reports. Proposed change (if any): 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~~ support product information change and/or trigger pharmacogenetic research.	Accepted.
338-339	7	Comments: Link is to the general EMA Pharmacogenomics guidance so doesn't directly point to source being considered in the guidance. Links may become outdated. Suggest referring to the specific guidance(s) considered in the text. Proposed change (if any): **remove hyperlink.**	Accepted.
338-339	8	Comment: The link is to the general EMA Pharmacogenomics guidance so it doesn't directly point to source being considered in the guidance. Links may become outdated. Suggest referring to the specific guidance(s) considered in the text. Proposed change (if any): **Remove hyperlink.**	Accepted.
344-345	7	Comments: Refer to guidance by title to avoid outdated links.	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): remove hyperlink.	
344-345	8	Comments: Refer to guidance by title to avoid outdated links. Proposed change (if any): Remove hyperlink.	Accepted.
346	5	Comments: it is not clear what to do with “considerations”. Rather, recommendations or obligatory actions should be mentioned here, possibly complemented with considerations. Proposed change (if any): **change “considerations” into “recommendations”**.	The text is amended.
347-349	2	Comments: It is unclear in regard to the proposed ‘pharmacogenomics surveillance system’ whether the biomarker has already been identified, or whether a specific biomarker is still in research. If the actual biomarkers have already been identified and are present in the label of the drug, it can be considered **routine care** to determine the patient’s genotype prior to treatment initiation. Please **consider to rephrase / further clarify** this section.	The text is amended.
347-349	2	Comments: It is noted that in many academic hospitals or other clinical settings, biological samples are already stored in biobanks. The efforts might therefore be particularly focussed towards identifying the **existing biobanks,** making use of the existing **infrastructure**, and ultimately **combining data** from different biobanks.	The text is amended.
349	8	Comments: We suggest adding the following words to the sentence to provide a concise description about dosing adjustment (if not on the drug label). Proposed change (if any): Dosing is adjusted by genomic BM **per**	This part of the document is amended based on other comments received.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		physician's best judgment.	
350-354	4	Comments: The guidance notes that the MAH should consider collection of a DNA sample from patients receiving a medication and experiencing serious ADRs or lack of effectiveness, especially in the initial post-authorisation period. This will be feasible in the clinical trials setting but **challenging** outside of clinical trials to obtain PGx samples from individuals reporting post-marketing ADRs. Furthermore, within **post-authorisation clinical trials**, measurement of drug **concentrations** in patients who experience serious ADRs may provide useful information.	This part of the document is amended based on other comments received.
351	5	Comments: "…it should be encouraged that genomic samples be collected (for patients that experienced ADRs)…" This could in our opinion be phrased more strongly. Proposed change (if any): "…it is **recommended** that genomic samples are collected from patients that experienced ADRs…"	The text is amended.
352-354	8	Comments: Lack of efficacy may be due to poor compliance rather than genomic influences. A genomic signal associated with lack of efficacy may not be observed in an association study if non-compliant subjects were included in the analysis. Efficacy associations are best studied in carefully controlled trials. Suggest deleting "initial post-authorization period", since many ADR during this period will be spontaneous reports, limiting the ability to obtain genomic assessment/information. Proposed change (if any): "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~~".	Not accepted. The issue is acknowledged, but not following situations of lack of efficacy would mean potentially missing a lot of relevant information. This part of the document is amended based on other comments received.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
355	5	Comments: Along the same line, biobanking should not just be considered, but recommended. Proposed change (if any): change “considerations” into “**recommendations**”.	The text is amended.
355-356	8	Comments: At this time, the bio-banking approach may not be a viable option due to views/opinions of ethics board governances. Proposed change (if any): “Collaborative actions, such as a consortium (biobanking)-based approach involving MAHs, academia and regulatory authorities should be considered **following review with appropriate ethics board governances**.”	This part of the document is amended based on other comments received.
360-361	4	Comments: The guidance refers to “internationally recognized pharmacogenetics/pharmacogenomics terms (including those included in MedDRA)”. It would be helpful if the guideline could **clarify** this statement. Is the agency referring to adverse event terms for which genomic BM have been identified for some medicines (e.g., hypersensitivity, SJS/TEN) or specific genomic terms?	The text is amended.
362	5	Comments: from all these considered actions, it is not clear what should be done with the outcome. To be published? Taken up in drug label? Reported to EMA/FDA? Proposed change (if any): **State more clearly what should be done with the outcomes**.	The text is amended.
364-399	8	Comments: The guideline should indicate that as technology is constantly evolving, a description on possible pharmacogenomic methodologies is outside the scope of this paper. Also, the same (or similar) comment in the scoping section of guideline could be included.	The text is amended. In addition, “methodologies” is removed from the title of this Guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): We suggest adding the following sentence: "**As technology is constantly evolving, a description on possible pharmacogenomic methodologies is outside the scope of this paper**".	
377-383	8	Comments: It is not clear how to implement the testing required for idiosyncratic reactions. To understand the properties of a biomarker, one would need to consider the effect of size and power when outlining the safety plan. Furthermore, the evaluation of biomarker performance (PPV and NPV) requires prospective studies. Proposed change (if any): "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, **and this can be done retrospectively (if samples exist) or prospectively**. When evaluating the performance of the BM, **prospective studies are required and** 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)."	The text is amended.
385	4	Comments: The guidance recommends evaluation of genomic biomarkers related to PK (e.g., transporters such as SLCO1B1). It would be useful if the guideline can provide **example** product labelling that references transporter genomic biomarkers. We are unaware of a validated test method for SLCO1B1 polymorphism detection (i.e., CE mark) that would support the use of SLCO1B1 in	The example of transporter BM SLCO1B1 is described shortly with simvastatin. However, test method is not commented as it is not the focus of this guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		patient care. Please could the guideline include an **example** of a validated test method for evaluation of transporter polymorphisms?	
388-389	8	Comments: The size of PK/PD study may not provide a robust answer regarding predictive value of a BM. Proposed change (if any): When evaluating the predictive value of the genomic BM, the sensitivity and specificity of the testing should be presented **if justified by study size**.	The text is amended.
390	8	Comments: At this time, the science has not evolved to make accurate assessments of metabolic phenotypes (many confounding factors). Furthermore, idiosyncratic reactions are not directly linked to plasma. Proposed change (if any): Remove the following sentence "~~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~~."	The proposed deletion is not accepted. It is stated "as relevant" which refers to situations where TDM is useful.
392-395	7	Comments: Text corrections. Proposed change (if any): Therefore, as relevant, assessing the ~~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~~ optimize dosing.	Accepted.
392-395	8	Comments: Text modification for clarity. Proposed change (if any): Therefore, as relevant, **assessing the** ~~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	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		well defined cases the genomic BM may help ~~optimal~~ optimize dosing.	
398-399	7	Comments: In some cases, the risk increase associated with the BM will be able to be provided in relative but not in absolute terms. Proposed change (if any): The risk increase in patients with the genomic BM should be presented in relative as well as absolute terms where possible.	Accepted.
398-399	8	Comments: In some cases, the risk increase associated with the BM will be able to be provided in relative but not in absolute terms. Proposed change (if any): The risk increase in patients with the genomic BM should be presented in relative as well as absolute terms **where possible.**	Accepted.
400-421 Section 5.3.2 Level of Evidence	8	Comments: This section should be followed by one addressing clinical diagnostic development. Simply because one has reason to believe that a specific variant may impose an effect does not mean that it should immediately be adopted. Accurately assessing genetic variants in a robust and reproducible manner requires sophisticated planning, testing, and validation. To make patient treatment decisions based on genetic testing in the U.S., for example, requires an Investigational Device Exemption of the test from the FDA Centers for Devices & Radiological Health and Drug Evaluation & Research. The authorization must be obtained prior to use of a test in a clinical setting. This section of the guidance may give the incorrect impression that any test can be used to make patient treatment decisions, which is not the case. Proposed change (if any): It is recommended to include a section on **diagnostic development to ensure the consistency and quality**	Not accepted. This is out of the scope of this guideline. This guideline is intended for the EU. The FDA example is not valid in the EU. (The updated IVD directive, that we are waiting on, is referred to.)

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		of genetic testing.	
406-407	7	Comments: The outcome prediction is of importance to multiple stakeholders including patients, families, payers etc. Proposed change (if any): …predict outcomes considered important to patients and ~~their families~~ other stakeholders.	Accepted.
421	7	Comments: Does this refer to impact on labelling guidance? Proposed change (if any): The impact of the genomic BM on labelling guidance will depend on the level of evidence and clinical relevance.	The text is amended.
424	5	Comments: As recommended by ESPT, the label of generic drugs should also contain the pharmacogenomics informations (Albertini. and Al. Recommendation of the European Society of Pharmacogenomics and Theranostics. Drug. Metab. Drug. Interact. (2012) 27(2):119.	Not accepted. Implementation of labelling change for products including generics will be the usual regulatory procedure for signal, PSUR, and referral, etc.
426	7	Comments: The inclusion in labelling should reflect both the strength and conclusiveness of the evidence. Proposed change (if any): …the level strength and conclusiveness of the evidence.	Accepted.
426	8	Comments: The inclusion in labelling should reflect both the strength and conclusiveness of the evidence. Proposed change (if any): The level of **strength and conclusiveness** of the evidence.	Accepted.
432	8	Comments: the strength of evidence is critical for the subsequent actions. Proposed change (if any): "For example, if **there is strong enough**	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		pharmacogenomics **evidence that** ~~if the pharmacogenomic information~~ alters….”	
439-441	7	Comments: Either remove comment on “*Evidence based information/recommendations … on the efficacy and safety consequences expected*” or provide more detailed guidance.	This part of the Guideline has been amended.
440	8	Comments: It is not clear what is meant by providing information for clinical decision making. We suggest the following text. Proposed change (if any): Evidence based information/recommendations regarding pharmacogenomic testing can be classified as 1) ~~for~~ providing information ~~for~~ **to enable** clinical decision making, 2) recommended or 3) mandatory.	This part of the Guideline has been amended.
442-444	7	Comments: Consider moving content of Annex 1 directly into the guideline text.	Not accepted.
446-448	8	Comments: Line 446~447 can be interpreted as conducting studies are the preferred way of effectiveness assessment Proposed change (if any): **Take the paragraph in line 446~447 out**. Begin with 448: “Evaluation of the….is necessary, **including the studies if they are deemed essent**ial. The objective is to establish whether the medicinal product use guided by the genomic BM has been effective or not;	The text is amended.
457-461	7	Comments: Remove example of study evaluating the effectiveness of risk minimisation measures or shorten and provide specific guidance. Proposed change (if any): delete text.	The text is shortened.
457-461	8	Comments: The example provided for evaluating the effectiveness of risk minimisation measures does not provide impact of the study. We	See above comment. The text is shortened.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		suggest **adding the following statement after line 461**. Also, it would be helpful to describe if additional studies were required to update the label. Proposed change (if any): "**The pharmacogenomic association studies for carbamazepine were conducted in the post authorisation period and the Boxed Warning, Warnings and Precautions sections of the carbamazepine label has been updated with this information".**	
465	8	Comments: The guideline should provide a more descriptive definition of allele. Proposed change (if any): ~~DNA sequence at a given locus of a particular gene.~~ "**one or more alternative forms of a gene that are found at the same place on a chromosome**".	Accepted.
481-485	9	**Internal proposed change (if any)**: Please replace this by wording from GVP Definitions Annex: **Pharmacovigilance: Science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem (see WHO).** In line with this general definition, underlying objectives of pharmacovigilance in accordance with the applicable EU legislation for are: preventing harm from adverse reactions in humans arising from the use of authorised medicinal products within or outside the terms of marketing authorisation or from occupational exposure; and promoting the safe and effective use of medicinal products, in	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		particular through providing timely information about the safety of medicinal products to patients, healthcare professionals and the public. Pharmacovigilance is therefore an activity contributing to the protection of patients' and public health.	
52-53	8	Comments: Variability in drug therapy could be due to a number of factors which may include gene-environmental interactions. Variable drug response may or may not include genetics, thus the sentence "mostly due to gene-environmental interactions" may not be accurate for every situation. Proposed change (if any): "There is large inter-individual variability in the response to drug therapy – in terms of both efficacy and safety, ~~mostly due to gene-environmental interactions~~."	Accepted.
539	6	The introduction of the special subsection about pharmacogenomics within the **section 4.5** of the SmPC could be considered with the aim of improving clarity of the information.	The text is amended.
555 Annex 2 comments	4	Comments: For the **abacavir** example, The lower range of prevalence phenotype is missing (**blank** to 8%) Please replace "serious" with **severe and bracket** to be consistent with the column heading Proposed change (if any): please refer to suggested wording in the comment.	The text is amended.
555 Annex 2 comments	4	Comments: For the celecoxib example, the implicated gene is **CYP2C9** not CYP2C19. Furthermore, the population allele frequencies included in the table represent CYP2C19 frequencies rather than	The text is amended.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		frequencies of the implicated gene, CYP2C9. Proposed change (if any): **please correct the gene name and allele frequencies in the annex.**	
555 Annex 2 comments	4	Comments: It might be helpful to include **clopidogrel** and CYP2C19 in Annex 2 since this example is referenced in section 4.1.1.	The text is amended.
56	8	Comments: The guideline could provide more clarity in the following sentence: “These genomic variations may relate to drug disposition (pharmacokinetic, PK) or drug action (pharmacodynamics, PD) or to individual’s susceptibility.” The meaning of individual’s susceptibility is not clear. Proposed change (if any): “These genomic variations may relate to drug disposition (pharmacokinetic, PK) or drug action (pharmacodynamics, PD) or to individual’s susceptibility to develop adverse reactions”	Accepted.
57	7	Comments: Suggest to use consistent expression for “benefit:risk” balance or profile. Current version uses **benefit/risk,** benefit-risk and benefit risk. Proposed change (if any): Use consistent expression.	Benefit/risk will be used.
65-66	8	Comments: The guideline could provide more clarity for the following sentence: “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.” It may be possible that genomic factors identify sub-populations with increased risk of side effects or reduced efficacy. Proposed change (if any): “The identification of sub-populations with	The text is amended.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		either increased or decreased sensitivity to medicines due to genomic factors could modulate ~~reduce both~~ the risk of side effects and the risk of lack of efficacy in those sub-populations."	
69-77	8	Comments: Guidelines for Oncology Pharmacogenomics are not provided in this document. A specific Reflection paper on pharmacogenomics in oncology is under development by the EMA since 2008. Therefore, for clarity, we would suggest to exclude oncology from the scope of this guideline and to add a reference to the Oncology PGx document. Proposed change (if any): To be added following line 77: "Oncology is excluded from the scope of this guideline as pharmacogenomics in oncology is addressed in the EMA Reflection paper on pharmacogenomics in oncology (EMEA/CHMP/PGxWP/128435/2006)".	"Guideline on the evaluation of anticancer medicinal products in mandated 13 December 2012, EMA/CHMP/205/95/Rev.4" is referred to.
Annex 1, lines 537-538	8	Comments: Some place holder text should be added within Annex I for section 4.4 of the SPC to include information, if any, regarding any strong correlation between ethnicity and ancestry with prevalence of particular phenotype or genotype. Proposed change (if any): We recommend adding the following text between line 537-538: "**Section 4.4: Any information on the prevalence of particular phenotype or genotype in any ethnic population that warrants an alert for a risk in response to a drug therapy (in terms of either efficacy or of specific AEs or lack of efficacy or safety) in that population may be provided here**." Cross-reference to section 5.2 should be added.	The text is amended.
Annex 1, after line 554	8	Comments: Within Annex 1 for section 5.2 of the SPC, if there is a need to add an alert for a risk in response to a drug therapy in any specific ethnic population, a cross-reference to section 4.4 should be	Accepted.

<table>
<tr><th>Line no.</th><th>Stakeholder no.</th><th>Comment and rationale; proposed changes</th><th>Outcome</th></tr>
<tr><td></td><td></td><td>recommended.

Proposed change (if any): We recommend adding the following text as continuation of line 554:

“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.</td><td></td></tr>
<tr><td>Annex 1, following line 542</td><td>8</td><td>Comments: Within Annex 1, after line 542, we would recommend adding in a placeholder for recommendations to be included in Section 4.6 of the SPC regarding the potential effect of genomic factors in pregnancy or in breastfeeding infants. We recommend using the example provided back on lines 222 to 224 of the guidance whereby fatal outcomes have been reported with opioid use in breast fed children of mothers who are ultra-rapid metabolisers (UMs).

Proposed change (if any): We recommend adding the following text after line 542: <u>“Section 4.6:</u> 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.</td><td>Accepted.</td></tr>
<tr><td>Annex 2</td><td>8</td><td>Comments: Celecoxib genomic marker is CYP2C9 and not CYP2C19. The allele frequency for CYP2C9 is shown below.

<table><tr><th>CYP2C9</th><th>African American (n=600)</th><th>Asian (n=204)</th><th>Caucasian (n=212)</th><th>Hispanic (n=202)</th></tr></table></td><td>The text is amended.</td></tr>
</table>

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		<table><tr><td></td><td>Freq</td><td>Freq</td><td>Freq</td><td>Freq</td></tr><tr><td>***1 (WT)**</td><td>**0.867**</td><td>**0.922**</td><td>**0.788**</td><td>**0.822**</td></tr><tr><td>***2**</td><td>**0.028**</td><td>**0.029**</td><td>**0.151**</td><td>**0.069**</td></tr><tr><td>***3**</td><td>**0.02**</td><td>**0.039**</td><td>**0.057**</td><td>**0.064**</td></tr></table> n:# of alleles Scott et al. Pharmacogenomics2010 June ; 11(6): 781–791 CYP2C19 to CYP2C9 and update MAF table. Proposed change (if any): Change genomic marker for Celecoxib from	
Annex 2	8	Comments: In the column “label”, link to SmPC sections that are impacted is **not exhautive**. Ex: abacavir, sections 4.4 and 5.5 are impacted as well.	“4.4” is added.