14.9.2016

Submission of comments on 'Guideline on good pharmacogenomics practice’ - EMA/CHMP/268544/2016

Comments from:

| Name of organisation or individual |
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| On behalf of EFPIA and EBE – Tiia Metiäinen (tiia.metiainen@efpia.eu) |

*Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.*

*When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).*

1. General comments

| Stakeholder number  *(To be completed by the Agency)* | General comment (if any) | Outcome (if applicable)  *(To be completed by the Agency)* |
| --- | --- | --- |
|  | EFPIA welcomes the opportunity to provide comments on the draft on “Guideline on good pharmacogenomics practice – EMA/CHMP/268544/2016”  We have a number of general and specific comments to be addressed in the forthcoming finalised guideline. |  |
|  | **Scope**  The document’s stated aim is to articulate requirements related to the choice of genomic methodologies so as to increase usefulness of genomic data from clinical trials. The context of “usefulness” is further explained as the implementation of pharmacogenomics (PG) into drug development and patient treatment. This is a worthy aim and is well laid out in the Executive Summary.  However, it would be highly appreciated if the agency would take into account the following concerns in order to offer added value to the drug development community and to improve the field:   1. The document is written in such a way that it is difficult to understand who the target audience is and what specific recommendations are for drug developers. Does this guidance apply to classical pharmacogenetics work, genome wide pharmacogenomics, or both? It was not clear what is included between the scope and the body of the document. The discussion regarding incidental findings was somewhat confusing if pharmacogenomics research is included in this guidance, because WGS/WES are used routinely to answer research questions, but these don’t often lead to identifying disease risk. The exploratory research assays are not conducted in a “Clinical Laboratory Improvement Amendments” type environment, therefore the findings might require verification on an approved clinical assay. 2. The draft guidance seems heavily influenced by EMA and pharma experience with drug metabolism enzyme and transporter pharmacogenetics. However, the guidance should be more encompassing of the expanding use of genome-wide pharmacogenomics, beyond drug metabolism, in drug development. 3. In general, the document appears to not reflect deep and recent experience in conducting PGx studies to support drug development (as evidenced by: The focus on candidate genes as opposed to genome wide approaches; focus on tumour driver mutations as opposed to other genetic variation; lack of attention to comprehensive drug related phenotypes other than PK, the suggestion that sequencing results must be independently validated with orthogonal method, etc.) 4. The author(s) seem to favour candidate gene approaches. While still employed in specific contexts (ADME PGx for example), genome-wide approaches are becoming increasingly more prevalent (and more powerful). The author(s) might consider laying out a framework for the document like this    1. Candidate gene approaches       1. Candidate gene methodologies       2. PK variability/ADME as an example    2. Genome wide approaches       1. Genome wide methodologies       2. Phenotypes of interest inclusive of surrogate markers, efficacy endpoints, safety, etc   The recommended approaches in this Guidance are not used or accepted scientifically today. |  |
|  | **Legal Basis and relevant Guidelines**  **ICH E18**  ICH E18 on genomic sampling and management of genomic data released for public consultation in December 2015 provides a strong framework for pharmacogenomic practice, while maintaining flexibility for pharma and regulatory agencies. Many of the topics in this draft EMA guidance have been addressed in the new ICH E18 guidance (e.g., sample collection and storage; assay development; sample analysis; etc…). This draft EMA guidance is very prescriptive and may limit development and adoption of pharmacogenomics by pharma, particularly as this area is rapidly evolving. For example, instruction provided in Sections 7.1 and 7.2 on Preanalytics and Analytics is considered narrow in scope, incomplete, and risks rapidly becoming out of date. Alternatively, the general approach taken in ICH E18, allowing for continued investigation and discussion between pharma, academia, and regulatory agencies, while emphasizing the need for quality consistent with the stage of drug development, is welcomed. The objectives of this new EMA guideline, in relation to ICH E18, should be clarified. It would be worthwhile to include any relevant references to this ICH Guideline in the final EMA Guideline. |  |
|  | **Common and rare genetic variants**  From a drug development perspective genetic approaches are used to explain clinical variability. Variability due to extremely rare variants is important but generally there is not enough power to make robust conclusions about the associations in clinical development studies. Therefore it is suggested to delete the proposed section common and rare genetic variant in the body of the document.  The interest of broad pharmacogenomic testing should be clarified. The guideline recommends at several occasions broad sequencing approaches in order not to exclude “rare” variants” affecting drug safety and efficacy but, at the same time, limitations of genotype versus phenotype with respect to drug PK are recognised. |  |
|  | **Study Design**  The clinical trial design described in this guidance for a PG-directed trial is useful. However, there are other possible designs that should be considered as also described in another EMA guideline (Reflection paper on methodological issues associated with pharmacogenomics biomarkers in relation to clinical development and patients’ selection EMA/446337/2011). Also, the agency is encouraged to consider how PG-related data is obtained from clinical trials where PG is not a primary, or even a secondary objective. Issues such as use of laboratory designed tests (LDT) with differing levels of verification/validation; adequacy of statistical power, especially concerning rare alleles; complications in sample collection in multi-country studies; etc., should be on-going discussions between pharma, regulatory agencies and academia. |  |
|  | The goal of PG research in drug development is to characterize PG-based intrinsic factors that will impact the safe and efficacious use of new medicines. Characterization usually begins during preclinical investigation, leading to hypotheses to be tested in clinical trials. Generally, the hypotheses are further refined in early clinical development, with a transition to confirmation as more data is obtained. Both hypothesis generation and confirmation will influence clinical trial design through all phases of development, leading to validation of important PG biomarkers and their inclusion in clinical use of new medicines. This iterative process leading to validated biomarkers was well described in an earlier EMA guidance on the use of PK-related PG in early clinical development (Use of pharmacogenetic methodologies in the pharmacokinetic evaluation of medicinal products, EMA/CHMP/37646/2009). It is suggested that this draft guidance be structured to better reflect the iterative and longitudinal process of PG biomarker identification and validation throughout a drug development program. |  |
|  | **Analytics**  In general, the repeated recommendations for using multiple platforms are confusing. Once a method is analytically validated, it is not common practice to confirm the results with another method. If using multiple platforms in clinical practice is an expectation that will be challenging to achieve. |  |

1. Specific comments on text

| Line number(s) of the relevant text  *(e.g. Lines 20-23)* | Stakeholder number  *(To be completed by the Agency)* | Comment and rationale; proposed changes  *(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome  *(To be completed by the Agency)* |
| --- | --- | --- | --- |
| Lines 36-39 |  | Comment: Recommend using language aligned with Regulation 536/2014 with regard to clinical trial and clinical study.  Proposed change: Genomic data have become important in the evaluation of efficacy and safety of drugs for regulatory approval, and in guiding patient treatment **decisions**, **which also results** in inclusion of information regarding genomic biomarkers in drug labels where relevant. The integration of genomic biomarkers in clinical trials**/studies**, as well as the technology used, should follow certain principles in order to generate reliable evidence for decision-making and patient treatment. |  |
| Line 38 |  | Comment: It may be worthwhile to briefly distinguish the terms “genomic” versus “genetic” and how this terminology is being applied throughout the document. The terms appear to be used somewhat interchangeably, which is not a universally agreeable principle.  Ref: <http://www.nchpeg.org/bssr/index.php?option=com_content&view=article&id=95:genetics-vs-genomics>  Proposed change: Make a distinction between the terms “genetics” and “genomics” when used in the document |  |
| Line 41 |  | Comment: The sentence beginning with “*The influence of the biomarkers on the studies …*” is not clear.  Proposed change: Suggestion is to delete or re-word more clearly: “Genetic research in the context of clinical trials is inherently difficult because it is often a retrospective effort within a trial that is otherwise intended to demonstrate efficacy and safety in a patient population. Given this, careful attention is required when designing the technical experiment, developing retrospective analysis plans and interpreting the results”. |  |
| Lines 43-44 |  | Comment: Draft ICH E18 should also be cited, as it is referenced in chapter 7.1 |  |
| Line 49 |  | Comment: The use of “requirements” seems too strong in this case, because throughout the document all guidelines/suggestions are presented as recommendations and not something that must be followed.  Proposed change: Suggestion to change ‘requirements’ to recommendations’ |  |
| Lines 55-56 |  | Comment: *“(b) increasing awareness of the importance of rare mutations in drug response together with a comparison of the different methods for DNA sequencing”*  The focus on rare mutations is not really relevant in the context of drug development. Rare mutations are an important genetic feature and they do explain variability in drug disposition, efficacy and safety in individuals. However, due to the limited size of drug development programs, it is not possible to evaluate the impact of rare mutations on drug response.  Furthermore, the primary intent of conducting PGx research in a drug development program is to identify clinically meaningful effects of common genetic variation such that it would impact clinical use of the drug in a reasonably sized patient population. That is not to say that rare mutations are unimportant to the individuals harbouring them – indeed, effect sizes are often larger with rare mutations – but they are just not likely to be evaluable during drug development. |  |
| Lines 62-70 |  | Comment: The scope statement is confusing because it is not clear whether circulating DNA is in scope or not. It seems to be out of scope, but then is referred to later in the document (249-255). Also, there is no mention of research data in the scope even though that is also referred to later in the document. |  |
| Line 63 |  | Comment: The use of “requirements” seems too strong.  Proposed change: Suggestion to change ‘requirements’ to ‘recommendations’ |  |
| Lines 64-65 |  | Comment: *“The scope of this guideline comprises requirements related to the choice of appropriate genomic methodologies during the development and the life-cycle of a drug”. P*er the WHO Global Model Regulatory Framework for Medical Devices Including IVDS (MAY2016), lifecycle includes development.  Proposed change: “The scope of this guideline comprises requirements related to the choice of appropriate genomic methodologies **during the life-cycle of a drug** |  |
| Lines 71-110 |  | Comment: Suggestion to include reference to ICH E16 (Qualification of genomic biomarkers) as an additional reference. |  |
| Lines 113, 171, 182, 191, 567, 664 |  | Comment: Harmonize the terminology preferably to align with that used in the definition of Pharmacogenetics (line 664)  Proposed change: Suggestion to update terminology to “inter-individual variations” rather than: inter-individual differences vs. inter-individual variability vs inter-individual differences vs. inter-individual variability |  |
| Line 116 |  | Comment: “*This leads to a transition from population-based*”, Verb tense  Proposed change: This **has led** to a transition …. |  |
| Line 117 |  | Comment: “*both in clinical drug development and practice*”  Proposed change: both in drug development and **clinical** practice |  |
| Lines 123-124 |  | Comment: “*This primarily includes analyses of the germline (host) genome but also of the somatic genome of tumours, or of the genome of infectious agents”.*  Proposed change: This primarily includes analyses of the germline (host) genome**, the** somatic genome of tumours, **and/or** the genome of infectious agents. |  |
| Lines 126-127 |  | Comment: Before addressing the more general concept of how pharmacogenomics influence drug response, particularly in regards to drug metabolizing enzymes and transporters, there should be comment/guidance as to the most appropriate ways to assess the impact of genetic mutations to drug exposure. In this regard, other extrinsic and intrinsic factors should be controlled, such that any PK differences can be concluded, with confidence, as due to gene variation. Similarly the concepts of metabolizer status and fractional clearance by the polymorphic gene product (fm or ft) are defined and specified as the primary goal of the clinical trial.  One should not proceed to studies seeking to evaluate the association of pharmacogenomics of drug metabolizing enzymes and transporters with efficacy and safety endpoints without a fundamental understanding. When this is done, one achieves the outcome described in lines 144-162. |  |
| Lines 128-130 |  | Comment: “*However, in addition, a proportion of clinical studies conducted have resulted in ambiguous findings highlighting the importance of correct measurement, determination, interpretation and translation of pharmacogenomic data into clinical treatment.”*  Proposed change: However, **a proportion** of clinical **trials**/studies conducted have also resulted in ambiguous findings highlighting the importance of correct measurement, determination, interpretation and translation of pharmacogenomic data into *patient treatment decision*. |  |
| Lines 130-131 |  | Comment: there is no mention of inadequate sample size or lack of replication studies in the list of pitfalls.  Proposed change: Suggestion to include ‘inadequate sample size or lack of replication studies’. |  |
| Lines 131-140 |  | Comment: The list of pitfalls is not in any logic order.  Proposed change: Suggestion to include a listing in the order of design, study population, selection of biomarkers, assays and analyses. |  |
| Lines 132-140 |  | Comment: The pitfalls described are very challenging to understand as stated e.g. What is a non-relevant SNV? Is it meant phenotype identification or definition of phenotype? What’s a non-PGx design, not taking into account pharmacology?  Other major challenges for PGx studies, as follows, were not included: 1) sample sizes are too small i.e. power of study, 2) clinical endpoints are variable and qualitative and 3) studies often don’t take into consideration the influence of ethnic background.  In addition, the examples provided do not relate directly to the pitfalls.  Proposed change: Suggestion to improve clarity of this section, by describing the additional major challenges such as sample size, endpoints and ethnic factors. Finally, provide concrete relevant examples. |  |
| Line 133 |  | Comment: *“Analyses of non-relevant Single Nucleotide Variations (SNVs)”*  It is not clear what is meant by “analysis of non-relevant SNVs”. It is often the cause that initial genetic associations are made with SNVs that are merely “tags” for causal variants. This is a well-established element of genome wide association studies. However, association is not synonymous with causality. Mechanistic studies to understand the causal biology of a genetic variant associated with phenotype variation is often (but not always) a critical step.  Proposed change:Suggestion to change the wording as follows: “ascribing functional causality to a SNV that is associated with phenotypic variability”. |  |
| Line 140 |  | Comment: *“Failure to take into account the pharmacology of the drug in the design of the study”*  One does not need to take into account the pharmacology of the drug to conduct a genome-wide association study. That is the beauty of the approach. However, ascribing causality to a “hit” is difficult. This requires mechanistic studies to establish causal biology. Often the causal biology is directly related to the known pharmacology of the drug, however sometimes genetic variation causes phenotypic variation in response to drugs due to previously unknown biology. So, it would be a mistake to make the suggestion that one must design their experiments based on what they know about the drug pharmacology at the outset. Rather, the experiment might teach us more about the biology than we currently know. This is a delicate balance.  Proposed change: To delete the sentence. |  |
| Lines 141-143 |  | Comment: “*Genomic studies, irrespective of whether they are conducted by academia or industry and/or for research and/or regulatory purposes, should be conducted using good genomic practices which will enable data comparison, integration and most efficient use*.”  It would be helpful to clarify the audience of this EMA draft guidance. It is difficult to understand if the guideline is talking about the field in general or is trying to provide guidance specifically to drug developers on how to conduct pharmacogenomic experiments. |  |
| Lines 144-162 |  | Comment: Examples of PG use should be clarified.  This section equates for the most part to a need for harmonization in genomic practices with historical examples were discrepant results emerged from different studies.  Many of the studies were never designed in the first place to address a specific genetic hypothesis but were studies designed specifically to address outcomes related to efficacy and safety in non-genetically defined sub-populations with a post hoc analysis looking at candidate genes associated with response.  The discrepant results were due to a number of factors including different analyses conducted in different patient population with different risk profiles for events ethnicities etc. However this doesn’t mean we need harmonization. From a drug development perspective it is useful to look at the genetic impact of a variant in different populations and studies. The accumulating evidence from the work has led to some guidelines being developed and published. Some of the data from the TIMI trials led directly to label changes for clopidogrel. The PREDICT study is a good example but it was designed to address a specific genetic hypothesis. Most development trials do not include a powered genetic hypothesis but they are still useful for doing exploratory work and providing useful data for scientific and potentially regulatory decisions. The CYP2C19 example used is confusing because it is important to understand the PGx impact across different populations, and in fact this point is made later in the document.  Examples are provided without reference. This makes it difficult to put the examples in context.  In at least the clopidogrel example, there is now a large collection of data, most of which has been obtained post-marketing and which informs current clinical practice. The general statements in this section do not accurately reflect current understanding and application of PG to clinical use of the cited drugs. These statements do not consider the complexity of identifying and validating PG biomarkers over time utilizing an iterative process over many clinical and preclinical studies, as well as post-marketing experience.  Proposed change: Suggestion to rewrite this section as it doesn’t define why harmonization is needed. Perhaps what would be helpful is to describe the process and limitations in interpreting data.  1. Discovery of genetic variants associated with drug response or disposition are often conducted in a post-hoc manner using patient data and samples collected in the context of a clinical trial with primary objectives not related to genetics.  2. When post-hoc analyses identify a candidate “hit” (association between genetic variation and phenotype), it is important to validate that hit in a separate set of patients with a prospective hypothesis.  Suggestion to remove some examples and just state the pitfalls. If the existing examples continue to be used, provide references (such as the clopidogrel studies, vitamin K antagonists, and PREDICT-1 trial) and instruction not only on problems but also on solutions that were used to arrive at the current clinical practice, and recognition of the iterative process in their validation. |  |
| Lines 152-157 |  | Comment: This EMA draft guideline gives some background and references to studies that were not sufficiently powered. However, the document does not explicitly detail the need for sufficiently powered studies. This is especially important in any exploratory pharmacogenomics study assessment, such as examining PK variability with ADME genes.  Proposed change: Recommendation to detail the need for sufficiently powered studies. |  |
| Lines 168-187 |  | Comment: These lines refer only to PG effect on pharmacokinetics (PK), although the section header does not make this evident.  As technologies improve, the technical ability to evaluate rare variants will increase. However, it will not change the fact that in a given drug development program (<10,000 pts), it will be possible to discover variants only with relatively large effect sizes, without the opportunity to study rare variants in a statistically meaningful manner, and common variants are more impactful to a drug label than are rare variants.  Terminology is confusing since both “rare variants” and “rare mutations” seem to be used interchangeably.  Proposed change: Suggestion to delete this section. Insert PK in this header on line 168 if this paragraph is kept add definition of rare variant and rare mutation to this document. |  |
| Lines 170-172 |  | Comment: *“Recent analyses have revealed that up to 40% of all genetically based inter individual differences in drug PK originate in the distribution of rare mutations the pharmacogenes in different populations”.*  Pharmacogenes is an additional term only used one time in this guideline. It can lead to confusion.  No reference is provided for the statement. Reference for the statement starting with “Recent analyses…”.  Proposed change: Recent analyses have revealed that up to 40% of all genetically based inter individual differences in drug PK originate in the distribution of rare mutations **in different populations.** Suggestion to provide reference for the statement. |  |
| Lines 178-187 |  | Comment: It is not clear if it is proposed that routine PK assessments are stopped or substituted with genetic predictions for PK outcome. Sometimes when outliers in PK profiles are observed candidate genes are studied in the individual to determine if there is putative genetic cause. It is already known that individuals may harbour singletons that could be functional. These are only useful for interpretation from a discovery or causative perspective and these variants are so rare as probably not useful for labelling/regulatory perspective. Also platforms already exist that do genotype rare variants and sequencing is becoming more routine. So discovering putative functional variants is likely to become more routine but unlikely to provide useful meaning from a patient population perspective. Collating these discoveries in a database may help us assign functional significance.  Proposed change:Suggestion to rewrite and to clarify the objective of this section. |  |
| Lines 184-187 |  | Comment: The need to supplement genotyping with phenotyping to understand effects of new (rare) variant alleles on PK is a developing area of research. The utility of this approach should be considered in context of the stages of drug development, and growing understanding of functional genetic variants.  There is a difference between the understanding the genotype: phenotype correlation during drug development, when many sources of intrinsic and extrinsic variability are being investigated, and in clinical practice when drugs are generally prescribed for large populations. There are examples of drugs successfully used in clinical practice that are prescribed using genotype without phenotype.  Proposed change: Consider removing or modifying this statement to reflect current use of PG in drug development and clinical practice, where genotyping is sufficient. Consider what is expected in the life of this guidance with the potential need to develop genotype/phenotyping correlations for some allelic variants. |  |
| Lines 185-187 |  | Comment: Incorporation of a complementary PK phenotype into many clinical studies would be difficult to achieve given current clinical trial structures. As is pointed out in lines 207-210, it requires a probe drug and it is unclear how this could reasonably be incorporated into clinical trials for the purpose of accurately characterizing rare mutations. It is agreed that the existence of rare variants can have great significance to the individual patient or clinical trial subject. However, in clinical trials seeking to assess the relationship of genotype to PK or PD, this infrequent error in phenotype classification can be overcome with appropriate sample size and should be noted.  Proposed change: It is recommended that this section be reworded to take into account the inclusion of appropriate sample size to limit the effects of rare variants on phenotype classification. |  |
| Lines 188-227 |  | Comment: These lines refer only to PG effect on pharmacokinetics (PK), although the section header does not make this evident.  This section is too focused on ADME PGx, and specific gripes about ADME gene nuances. ADME PGx is one application of PGx research in drug development.   1. The usefulness of the paragraph comprised of lines 189-192 is questioned. 2. 194 – 198: Please provide references 3. There is a contradiction in that Lines 193-199 give CYP2D6 as an unreliable example where “phenotype is not identifiable by genotyping”, whereas Lines 218-221 cite CYP2D6 as a reliable example where “genotype variation can be predictive for the PK phenotype”. Also note that the predictability of a genotype on the phenotype (for metabolism genes) is dependent on the drug and the amount or fraction of the drug passing through enzyme. The relationships are complex if multiple pathways are involved but generally simplify when one gene is responsible for the phenotype. The complexity of the CYP2D6 gene in the genotype:phenotype discussion might be the best studied to date. For example, the recent publication of Shah et al., (Pharmacogenomics. 2016 Feb;17(3):259-75.) highlights difficulties with CYP2D6. Also, in line 225 phenotyping is recommended, not required as stated in line 198. 4. This is an example (Line 198) of the draft guidance being too prescriptive, indicating that phenotyping of CYP2D6 “must be carried out”, even indicating the use of debrisoquine or dextromethorphan as probe drugs. Several alternatives probes can be considered. 5. While there are challenges in extrapolating PK phenotype from positive identification from in vitro studies, it is significantly more difficult to identify the cause(s) of PK outliers without guidance from such in vitro studies, due to the number of other intrinsic and extrinsic factors influencing drug exposure. It is recommended to reinforce that in vitro studies are essential for basic understanding of metabolizer pathways for a compound of interest prior to in vivo assessment. It is recommended that the guideline considers discussing the importance of understanding the fraction of total clearance due to polymorphic pathways in early clinical trials, therefore controlling for the variable as cited in lines 200-204. 6. The paragraph comprised of lines 207-217 seems to be most related to the conduct of DDI studies and not PGx research. It is not clear what is gained by using “probe substance”; what is being proposed is very difficult to accomplish and may not be informative. How to use enzyme phenotyping studies in drug development has been covered by existing guidance on drug-drug interactions. It does not seem that this topic fits in scope for this guidance. 7. ADME PGx research is informed by preclinical phenotyping, but ultimately, clinical PGx studies are necessary to definitively ascribe a PGx effect to a drug/metabolic pathway. The existing knowledge is not sufficient to allow for data from a probe drug (for a specific metabolic pathway) to be used to ascribe a PGx effect onto another drug that may also be metabolized through that pathway. 8. Regarding point “ii) *having a specific, targeted, quantifiable metabolite”* the need of metabolite is questioned, this may introduce more complicating information. It may be sufficient to rely on the clearance of parent. Clearance/concentration of the probe should be the primary focus whereas data for a metabolite is more complicated to interpret: the observed metabolite concentration not only depends on the rate of formation (by the enzyme to be assessed) but also on its clearance which is a different process depending on different mechanisms. 9. 218-227: This statement indicates that 110 different alleles of CYP2D6 have been tested in vivo. This seems unlikely. Pointing out that genetic variation in the TPMT gene (for example) is not robustly associated with PK variation misses the point. Genetic variation in TPMT is very robustly associated with thiopurine metabolism and sometimes fatal toxicity of thiopurine drugs. Taken out of context, the paragraph, as written, implies that PGx of TPMT is not robust - -which is certainly not the case. Recommend to clarify why “*other gene products such as CYP2C9, CYP2C19, UGT1A1 and TPMT, have a less robust association between genotype and PK phenotype variation”* as compared to CYP2D6. The literature would appear to indicate otherwise   Accounting for all genetic variations within an individual is theoretically possible today, including variants already noted but also many others that will be found. However, understanding functional consequences of all allelic variations within a gene is difficult to imagine at this time. Studying individual rare variants in a population, especially in a drug development strategy, is probably impossible. It should also be considered that PK monitoring is not typically done in all clinical studies during drug development. Given current technologies and data management, it would be difficult to incorporate every known variant in a gene when conducting PK monitoring.  There are alleles that are well-known to be clinically actionable and that is fit-for-purpose for decision-making in the clinic which should be recommended, such as the class 1 PharmGKB list. As the guideline does not specify situations where clinical validation of genotyping with phenotyping should be performed, reference should be made here to the Guideline on the use of pharmacogenetic methodologies in the pharmacokinetic evaluation of medicinal products.  Proposed change: Suggestion to delete this section or to take into account the above mentioned comments if this section is kept e.g. Insert PK in this header on line 227 |  |
| Lines 228-271 |  | Comment:  There is little control in the sample received from an investigator site (Lines 241-242). It is not clear what the guidance recommends related to tumour heterogeneity. The example used is not representative of personalized medicine in oncology.  Identifying driver mutations are certainly one element of tumour genetic research, however not all genetic variants of interest in a tumour are driver mutations. For example, tumour mutation burden is a recent focus related to association with response to immunotherapies.  The liquid biopsy section (lines 249-255) does not acknowledge that the technology is still in its infancy. Probably too immature to be of use during drug development.  The usefulness of epigenetic section (lines 256-271) is questioned. In some cases methylation may be detected in blood (Line 269)  Proposed change: Suggest deleting this section or to take into account the above mentioned comments if this section is kept |  |
| Lines 251 |  | Comment:  *“The liquid biopsy can potentially address challenges relating to functional heterogeneity. This technique may also be useful when a tumour is too small to be visualised for biopsy*”.  The emerging importance of liquid biopsy in clinical genetics is strongly supported. However, it is important to mention here that existing technologies may not identify tumour mutations in all patients, as ctDNA shed into the circulation varies by disease, stage, and individual. It is also recommended to include other common uses of ctDNA technology, as below.  Proposed change: “The liquid biopsy can potentially address challenges relating to functional heterogeneity **and tumour evolution, in patients where there are detectable levels of ctDNA in the circulation.** This technique may also be useful when a tumour biopsy is *unavailable or inaccessible, or for serial evaluation over the course of treatment*.” |  |
| Line 264 |  | Comment: *“The extent of tumour drug resistance can be followed by examination of ctDNA using the liquid biopsy technique”.* Evaluation of ctDNA methylation states will likely have broader impact beyond studies of resistance.  Proposed change: Suggestion of the following alternative wording (perhaps it flows more logically in the Liquid Biopsy section?): “**Methylation states** can **also** be followed by examination of ctDNA using the liquid biopsy technique **to enable study of response and resistance.**” |  |
| Line 274 |  | Comment: *“Study relevant genomic variations, particularly those with functional importance”.*  The most powerful discoveries today are coming from unbiased genome wide approaches. If the guideline is suggesting that only candidate gene approaches are relevant to drug development, this perspective is not at all aligned with current drug development science or practices.  Proposed change: Further clarification would be appreciated |  |
| Lines 276-277 |  | Comment**: “***Validate critical sequencing results using, either an independent analytically valid method or resequencing a second amplicon of the same region*”  The requirement for using an independent platform to validate critical sequencing results is confusing. What is the definition of a critical sequencing result? Is an independent platform only required if the sequencing platform is not analytically validated? It would be challenging to routinely use multiple platforms in clinical practice.  The current state of NGS and Sanger sequencing is such that the results may be robust enough on their own, when generated in a regulated laboratory, to not require validation using an alternate technology. The draft guideline already references ISO, CLIA and CAP certifications for laboratories carrying out this work. Those regulations require a validation of any assay being run, from which a clear understanding of the assay robustness would emerge. We appreciate that whilst this may be good practice in some organisations, we understand the important that the issue of validation is stressed in this guidance.  Sequencing results are not to be validated on an orthogonal technology. The following is being done for the validation of sequencing results:   1. Discovery platform is employed for discovering genetic hits. At the time of selection of a discovery platform, the platform must be analytically validated (once). Once employed in experiments, data are analysed from a single platform. 2. If there are any “hits” (association between gene variant and phenotype), this result must be replicated in an independent set of patients/samples. 3. Replication will often use an orthogonal technology to the initial platform.   Proposed change: Suggestion to reword this section. |  |
| Line 278 |  | Comment: **“***Use published and well curated sequence databases with care and caution*”  Not sure what is meant here: is the context here applied to selection of a reference database? If so, this should be explicitly stated. There are many robust and well established reference databases available today. |  |
| Line 279 |  | Comment: “*Employ bioinformatics methods including algorithms of relevance and validate them*”  This statement is not clear enough. For the sake of the broader audience it would be valuable to include a reference here on how to validate bioinformatics methods. Not sure what is meant here: this is a vague statement.  Proposed change: Further clarification would be appreciated. |  |
| Lines 280-289 |  | Comment: Given the noted lack of predictability of current software programs, it is not clear what is being recommended or required in this paragraph.  Are PolyPhen-2 and SIFT recommended for use or not? This guidance does not address the tiers of data needed to determine reliable sources of information used to determine functional impact (i.e. ClinVar and similar databases).  Proposed change: Suggestion to provide clarity for this paragraph. |  |
| Line 288 |  | Comment: “*At present it is not advisable to consider available software for prediction of the functional consequences of missense mutations.*  Software based on accumulating evidence and collation of variants and phenotypes is generally the only route unless the guideline is suggesting performing a functional experiment. Although mutation analysis applications have their limitations, the statement that it’s not advisable to consider available software for prediction seems a bit strong  Proposed change: At present it **is recommended** to consider available software for prediction of the functional consequences of missense mutations **only in very rare cases**. Further clarification is needed on suggestions to perform predictions |  |
| Lines 290-299 |  | Comment:The meaning of “bigger genetic analyses” is not well understood. It is not in agreement with the guidance to avoid WES or WGS. This is becoming a standard approach yielding important new findings. To suggest that instead candidate gene approaches are preferred is not aligned with today’s approaches. There is no data to support the claim that performing WES vs WGS will result in reduced incidental findings, especially since WES would capture protein disrupting mutations. One could suggest keeping the analysis, not sequence generation, specific to the question being addressed. There is enormous power in conducting genome-wide research. Statistical approaches can be used to limit hypotheses to a restricted number of variants when and if supported by biological rationale. The comment also is a reference probably to some of the on-going dialogue on what to do when incidental findings (those not related to the primary hypothesis but which might be important for medical care are discovered) arise.  In recommending target-region NGS over WES and WGS to avoid incidental findings, it would be useful for the guideline to highlight the reduced complexity of data management and statistical power implications with the targeted approach thereby minimizing reference to incidental findings.  Proposed change: Suggestion to delete this section and to allow the field to continue this dialogue. This guidance should highlight the need for organizational processes and guidance around the possibility of incidental findings and could reference the iPWG paper on the topic. |  |
| Lines 301-321 |  | Comment:These recommendations have been well documented in many other guidances and publications.  Line 309, since companies like 23&me have made a business out of sequencing millions of people from saliva/buccal swab based DNA this sentence seems to conservative.  Proposed change: Suggestion to delete this paragraph or to reconsider the position taken on saliva/buccal swab if this paragraph is kept. |  |
| Lines 312-316 |  | Comment: Because of the complexities with coding, it would be appreciated if the agency would accept to include a recommendation of single coding. This is where much of the field is going and it is consistent with the draft ICH E18 guidance.  Line 316, it would be necessary to clarify as to whether this is referring to bioprobes or sample identity. In case it is referring to bioprobes it would be necessary to suggest mechanisms or steps for ensuring the identity of the bioprobe beyond any doubt, and certified, at a high standard.  Line 317-319. Regarding transport of samples to the site of analysis, it isn’t clear whether this may contradict national laws and/or requirements.  Proposed change: This is an example where ICH E18 is considered to provide adequate guidance on how to label and track PG samples, consistent with global ethical and regulatory requirements and without being too prescriptive.  It is recommended to clarify in the guideline (Line 316) as to whether this is referring to bioprobes or sample identity and to suggest mechanisms or steps for ensuring the identity of the bioprobe beyond any doubt, and certified, at a high standard, if applicable. |  |
| Line 321 |  | Comment: Formal SOPs (if that’s what the authors intended) are not required to ensure high quality preanalytics. Working guidelines/practices and adherence to them are sufficient.  Proposed change: Suggestion to not require formal SOPs. |  |
| Section 7.2, lines 322-434 |  | Comment: This section on analytics can be considered too prescriptive. Again, reference to ICH E18 is suggested, which indicates that appropriate technologies should be validated and applied to determine important PG components of drug exposure, safety and efficacy.  Proposed change: Suggestion to reduce this section, consistent in approach with ICH E18. |  |
| Lines 327-328 |  | Comment: ***“****It is also recommended that a second, independent (alternative platform) test should be used to validate the results of the genetic analysis.”*  During the discovery phase, it is not practical to repeat the experiment on an alternative platform. However, clinical validation of the result (that the association between genetic variation and clinical phenotype is real) in a different population may well employ a different platform. Perhaps the guideline intents to point out that when initially using a new platform it must be validated against an orthogonal platform– but after the platform has been validated, there is no need to do so for every experiment. This is impractical, not a good use of R&D resources and is simply not done.  Proposed change: Further clarification would be appreciated. |  |
| Lines 328-329 |  | Comment: **“***In clinical studies, another means of checking drug exposure such as therapeutic drug monitoring should be utilized*.”  It is not clear what is meant or suggested by this. During a clinical trial, there is a validated assay used to determine blood/urine (etc.) drug levels. This is not done on more than one platform. Nor would any regulatory agency want the data from 2 different platforms.  Proposed change: Further clarification would be appreciated. |  |
| Lines 329-332 |  | Comment: **“***It is expected that the analysis or the test should provide unambiguous results and that “rare” variants affecting drug safety and efficacy are not excluded (see section 4. Pharmacogenomic variants: phenotyping and genotyping).”*  Regarding the expectation that rare variants should not be excluded – this is not practical and not necessary. Genotyping platforms are a mainstay of genetic research and include only some rare variants. The only way to “not exclude” rare variants is to conduct whole genome sequencing and analyse the entire genome – which is not a reasonable expectation today.  Proposed change: Further clarification would be appreciated. |  |
| Lines 333-337 |  | Comment: Imputation is a mainstay of genetic research. As the reference databases get better, the ability to impute is remarkably good. Even in difficult genomic regions, such as the MHC complex, HLA haplotypes are imputable with > 99% accuracy.  Proposed change: Suggestion to delete as this not in line with where the field is at this time. |  |
| Line 333 |  | Comment: The authors seem to be cautioning the principal of linkage disequilibrium whereas this is well established. Highly polymorphic genes e.g. HLA would normally not fall into this category so this section isn’t very clear. Proxy SNPs are briefly discussed, but no recommendations are made regarding imputation of data particularly when multiple array types may have been used. The first measurement may be made from imputation, so stringency requirements should be discussed.  Proposed change: Please clarify the statement. |  |
| Lines 338-347 |  | Comment: This paragraph conflates several issues. Analytical validation of a platform is quite different than functional annotation of the findings, and also quite distinct from incidental findings. An incidental finding is one that was unexpected and/or not related to the original research intent (but may still be accurate and meaningful). The statement softens the earlier reference of the utility of SIFT and PolyPhen.  Proposed change: Suggestion to delete or to de-convolute the paragraph. |  |
| Line 350 |  | Comment: It is unclear what levels (e.g. average; overall) coverage the document is referring to, and it may be inadvisable with evolving technology to describe germ line mutation sequencing coverage limits. If those are described, somatic mutation limits should also be included, which would be difficult to specify in this document. This statement may be out of scope for this guidance. Proposed change: Suggestion to delete this statement. |  |
| Line 360 |  | Comment: Earlier recommendation in the document put forth targeted NGS but this section now clarifies that metabolizing enzymes are not amenable to that because of sequence complexity.  Proposed change: Please specify the recommended technology for these regions. |  |
| Line 364 |  | Comment: CNV abbreviation is missing  Proposed change: include abbreviation (CNV) |  |
| Lines 394-402 |  | Comment: *Intra patient verification of genotyping results*  It is not feasible and unnecessary to require verification of genotyping results during drug development, in contrast to replication. If data are to be returned to the patient or health care provider for clinical care decisions, perhaps. But that is a rare occurrence during drug development.  Proposed change**:** Suggestion to delete. |  |
| Lines 399-402 |  | Comment: *“The best strategy to avoid this is the employment of two independent (chemistry/technology) approaches in the very same patient, i.e. intra patient verification (IPV). Only when the two results of the IPV are identical, the results should be used. This applies to PGx analytics during drug development as well as for pharmacovigilance.”*  Most genotyping platforms are robust and have high fidelity. Several QC steps are usually integrated into the pipeline that can provide an estimate of accuracy. The density of SNPs may allow for understanding if the signal is real (i.e., peaks of SNPs generally not on the same area of the platform.) For meaningful results, Sponsors are likely to check some samples to see if the signal SNP is true but it is not necessary to run two independent chemistries. It should be clarified when Intra Patient Verification should be performed as it should be linked to the intended purpose of genotyping results.  Proposed change: Suggestion to delete the comment or to rewrite it as follows; The best strategy to avoid this is the employment of two independent (chemistry/technology) approaches in the very same patient, i.e. intra patient verification (IPV). Only when the two results of the IPV are identical, the results should be used. This **may apply** to PGx analytics during drug development as well as for pharmacovigilance **depending on the development phase and if the results are used for clinical decision making.** (cf. draft ICH E18 section 3.1). |  |
| Line 400 |  | Comment: Along with the comments above, two technologies per assay will be difficult to achieve (lines 267-277) and may be unnecessary if these are validated assays. |  |
| Line 408 |  | Comment: This statement is misleading. The most straightforward naming is genomic location + reference build number. |  |
| Line 426 |  | Comment: This section should highlight the importance of increased analytical rigor e.g. CLIA as the use of the data becomes more central to impacting patient safety or increases regulatory risk. Purely exploratory work doesn’t need the additional burden of CLIA/CAP certification |  |
| Section 7.3, lines 435-445 |  | Comment: This is an incomplete discussion of the development and use of sample repositories. It does not account for the ethical and legal difficulties associated with global collection of PG samples and their subsequent analysis and use of data.  Proposed change: Indicate the value of sample repositories, but acknowledge the difficulties in collecting, analysing and using data from those samples. |  |
| Lines 438-445 |  | Comment: “For retrospective analysis of such samples for PGx” .Not all retrospective analyses are for PK evaluation.  Proposed change: “For retrospective analysis of **pharmacokinetic** samples for PGx, the EMA guideline…” |  |
| Lines 462-481 |  | Comment: Recommend to mention sample size issue/limitation/solution in early phase studies. Study design partially depends on sample size. |  |
| Lines 463-464 |  | Comment: Predictive genomic biomarkers may be identified during early exploratory trials/studies, based on biological plausibility or non-clinical research. |  |
| Line 474 |  | Comment: This should be expanded as there are a number of things that can affect reproducibility of GWAS. |  |
| Lines 474-475 |  | Comment: Please provide a definition of “very strong association”. |  |
| Line 511 |  | Comment: What is meant by the word “forms”? |  |
| Sections 8.1 -8.3 |  | Comment: This area has been discussed in many other publications and guidances.  Proposed change: Suggest to delete / or cross-reference only. |  |
| Lines 524-557 |  | Comment: Currently the “Pharmacogenomic biomarkers and translation into the clinics today” only focused on HLA. It is inconsistent with the Header of this section.  Proposed change: It is recommended to add other type of example in order to strengthen the section. |  |
| Lines 549-550 |  | Comment: It states that clinical validation should show replication in different populations. Not clear what “different populations” refers to. If “populations” here refers to ethnic groups, it is possible that an association with a particular DNA variant might be demonstrable in only certain populations due to differing allele frequencies in different populations.  Proposed change: Could delete “in different patient populations”. |  |
| Lines 553-557 |  | Comment: It is recommended to move the HLA typing methods to previous sections relevant to analytic method since it will fit there better. |  |
| Lines 663-671 |  | Comment: In the draft guideline two definitions are given for Pharmacogenetics and Pharmacogenomics, according to ICH and to CIOMS VII. For clarity to the reader of the guideline it is proposed to use only the definition as given in ICH E15.  Proposed change: Pharmacogenetics – the study of variations in DNA sequence as related to drug response, a subset of pharmacogenomics (ICH E15)  Pharmacogenomics – the study of variations of DNA and RNA characteristics as related to drug response (ICH E15) |  |

Please add more rows if needed.