European Medicines Agency

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OVERVIEW OF COMMENTS RECEIVED ON DRAFT REFLECTION PAPER ON THE USE OF PHARMACOGENETICS IN THE PHARMACOKINETIC EVALUATION OF MEDICINAL PRODUCTS (EMEA/128517/2006)

GENERAL COMMENTS OVERVIEW

Overall, the paper was received well. The need and time for a paper on this subject was indicated in a number of comments.

The most important concerns that led to modification of the paper are summarised below:

Generally, it was indicated that we could more clearly state in the document that we are concerned about functionally relevant polymorphisms and not just any polymorphism. This aspect is now expressed more clearly in the revised document (section 3).

Statistics was indicated to be an issue in a number of comments. The number of patients needed to be screened in order to include in a study may be very large for a rare polymorphism. This aspect has been reflected in the revised text (section 3 and 5).

The fact that in vitro systems for metabolising enzymes are more mature than that of drug transporters was mentioned. This is agreed, and has been mentioned in the revised text. A role of transporters may become clear using combined data such as ADME data or renal excretion data (Section 4).

With respect to inhibition of metabolising enzymes it was indicated that consequences of inhibition may be more pronounced in a population with lower but not abolished activity. Although such a population is hard to define genetically, general information on this matter has been included in the revised document (section 7).

It was indicated that the age groups where differences in enzymes and transporters as compared with adults are most pronounced should be defined more explicitly. The age groups were specified according to the ICH guideline (CPMP/ICH/2711/99): newborn infants, infants and toddlers (0-2 year old children). Furthermore, it is indicated that also in the very elderly patients PG related differences in metabolism may occur and have an impact due to potential impaired functionality of system/organs. However, currently limited knowledge on this aspect is available (section 8).

Throughout the document, minor linguistic changes were implemented, mainly to improve focus and to further clarify the observations which drives the need for performing PG/PK studies.

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Table 1: Organisations that commented on the draft Guideline as released for consultation

	Name of Organisation or individual
2	Bristol-Myers Squibb
3	Merck Sharp & Dohme (Europe) Inc
4	TEDDY Network of Excellence
5	Dept. of Biochemistry and Medical Biotechnologies University Federico II of Naples, CEINGE- Advanced Biotechnologies, Naples- Italy
6	Schering-Plough
7	Czech Republic Medicinal Board
8	EFPIA

Table 2: **Bristol-Myers Squibb**

GENERAL COMMENTS - OVERVIEW
We appreciate that EMEA has been paying close attention to the emerging role of pharmacogenetics in drug development. This reflection paper is a timely document for the pharmaceutical industry to understand the current view of the agency. The overall scope is appropriate and timely, and the proposals in this paper are forward thinking. This paper clearly illustrates the current opportunities and challenges, as well as the future direction of this area. Generally, we agree with your view that the studies proposed in this paper will greatly facilitate the understanding of interindividual PK variability. However, we believe that some of the recommended studies here are not feasible or come with little added values, partly due to the gap between the large sample size typically required for a meaningful genetic study and the relatively small sample size of PK studies. The examples of such cases are described in detail in the next section.
Overall, BMS agrees with the intent of the reflection paper, but we believe that the paper could strike a better balance between the current state of the art and what is achievable in a practical setting. BMS appreciates the opportunity to provide comment and respectfully requests that EMEA give consideration to our recommendations. We would be pleased to provide additional pertinent information as may be requested.

SPECIFIC COMMENTS ON TEXT		
SECTION 3 **The situation in which the effect of PG on PK should be studied**		
Line no. + paragraph no.	**Comment and Rationale**	**Outcome**
	In Section 3 of the paper, the first sentence states "PG studies are required for PK evaluation of a new chemical entity if polymorphically expressed proteins are known to be involved in important pathways of metabolism or transport of this compound or pharmacologically active or toxic metabolites, and therefore significantly affecting the local systemic exposure to these substances." We agree with this statement, in cases where a drug is known to be metabolized or transported primarily by a functionally polymorphic protein such as CYP2D6. However, we do not believe that a PG study is always necessary, even when a polymorphically expressed protein is known to be involved. The following are some of the examples we consider to be exempt from such a requirement. • A metabolism enzyme is not functionally polymorphic. Many of the protein polymorphisms appear functionally neutral, or only cause subtle functional alteration. A regulatory requirement for PG studies should be at least limited to those cases where a polymorphism with a significant functional alteration is known, such as in the case with CYP2D6. • Even when a functionally polymorphic protein such as CYP2D6 is involved in the metabolism, PG studies should not be a requirement, if it is not the primary drug metabolism enzyme for this drug. • And even when a functionally defective polymorphism/mutation is known for an enzyme, which is involved in the primary metabolism pathway, the requirement for PG should be limited to the cases when this polymorphism is relatively common in the population. For example, if a particular polymorphism/mutation is extremely rare, it is difficult to conduct a sufficiently powered PG study to address the effect of this polymorphism/mutation on PK.	PG studies are not required if the genetic variation does not translate into significant differences in protein activity (or expression) involved in a major pathway of elimination or formation of pharmacological substances contributing to efficacy/safety. This can be clarified more in the text and the sentence in section 3 has been modified to ... "*Studies of the effect of PG on PK are required for PK evaluation of a new chemical entity if the genetic variation is likely to translate into important differences in the local and systemic exposure to this substance or its active or toxic metabolites.*" 2:nd bullet point: As pointed out, the sentence states " important differences". This will include major pathway(s) of drug elimination as well as major formation and elimination pathways of active (or toxic) metabolites. This has now been further detailed by " *PG variants may impact on Absorption, Distribution, Metabolism and Excretion of the compound.*": 3:rd bullet point: We agree that it may be difficult to study polymorphisms which are extremely rare. The metabolism and transport consequences of drug therapy could however

		be fatal if erroneous dosing is carried out in a specific patient carrying a rare polymorphism. It is difficult to set a frequency-limit in this case, which must take the consequences into consideration also. The default should be to study the polymorphisms in clinical studies and phase I studies. The applicant should justify absence of such data. This may include difficulties in recruitment of individuals with a gene variant of very low frequency. However, lack of data may be reflected in the labelling if considered relevant. This has now been further clarified in the document, by inserting "*Although some polymorphisms are extremely rare, the applicant should always consider studying the PK and clinical consequences of all potentially clinically relevant polymorphisms. If this is not feasible, the applicant should justify the lack of data and discuss the possible safety (or efficacy) consequences based on prior knowledge on the effect of the polymorphisms on protein activity. Lack of data should be reflected in the Summary of Product Characteristics (SPC) if considered clinically relevant.*"

	The second paragraph states "PG studies involving the identification of novel polymorphic loci are encouraged to be carried out if the compound exhibits important interindividual PK variability, without evident known genetic explanations, likely to affect clinical efficacy and safety. Technology has advanced to the point that analysis of genetic factors affecting safety and efficacy of medicines is now fast and reliable." We agree that the technology has advanced enough to genotype DNA polymorphisms quickly and reliably. However, this technological advance still does not warrant that we can set up and complete a sufficiently powered PG-PK study in a timely manner. Typically PK studies have a relatively small number of patients, while PG studies to discover novel genetic factor require a much larger number of patients. Thus, is it usually difficult to set up a meaningful PG-PK study with the goal of discovering a new genetic factor affecting PK. This is the case despite the technical advances in genomic analyses, because the genotyping technology itself is not the rate limiting step. Because of these reasons, we think this type of PG-PK studies can be recommended, but should not be required.	We agree, and do not state that this kind of study is required, only that it is encouraged.

Recommendation for the PG sample collection		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	We agree with the following statement from Section 3: "In all cases where unexplained PK variation has been identified, samples for pharmacogenetic purpose in further clinical trials, should be collected for future analyses." This approach would facilitate the conduct of a useful post-approval analyses, and would provide important prescribing information to be generated without restricting the availability of a potentially useful new medication.	No comment necessary

SECTION 5 **Study design and methodology**		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	In Section 5 of the paper (STUDY DESIGN AND METHODOLOGY), the recommendations made are very general and fail to fully account for the difficulty in conducting the proposed studies and analyses. For instance, the recommendation to evaluate the effect using population PK fails to consider the number of patients required in the complete dataset and the number of subjects expressing the polymorphism of interest. Typically, a polymorphism occurring in about 30% of the subjects would be identifiable as a covariate in a study containing 100 patients. For a rare phenotype (1%), data from about 3000 patients would be required to identify the polymorphism as a covariate. It may not be possible to collect data of sufficient quality in such a large number of subjects to allow the identification of a rare polymorphism. It would be useful for EMEA to consult with a pharmacometrician to provide a recommendation that would thoroughly consider the logistics of this approach. Likewise, a "conventional" PK study would suffer from the same limitations based on the percentage of the population expressing the rare phenotype.	We find it difficult to be more specific and to make statements which would be valid for all scenarios. Still, we have modified the section as follows: "*In both cases the study should include a satisfactory number of patients of each genotype in order to obtain valid correlation data. Power calculations should preferentially be done before the initiation of the study to ensure a sufficient study size. If a genotype is rare, phase I studies with selected inclusion of subjects of this genotype could be useful if feasible. It is acknowledged that stratification by genotype is difficult for very rare genetic variants but in many cases the effect of a particular rare genetic variant could be large and influences the specific treatment substantially.*"

SECTION 7 **Special consideration related to drug-drug interactions and impaired or immature organ functions**		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	Finally, in Section 7 of the paper (SPECIAL CONSIDERATION RELATED TO DRUG-DRUG INTERACTIONS AND IMPAIRED OR IMMATURE ORGAN FUNCTIONS), the recommendation assumes that the subject population would be readily identifiable and studied. Since it is unlikely that sufficient numbers of subjects would be available, we are uncomfortable with the recommendation to speculate on the effect of impaired or immature organ function on the PK of a drug substance. In addition, it would be helpful to characterize the groups (newborn infants, infants and toddlers) by age.	We agree that it may be difficult to study this. Therefore we only recommend that this should be discussed and reflected in the labelling. As clearance via parallel pathways of elimination are additive, knowledge about the PK effect of the polymorphisms in patients without impaired organ function, contribution of renal clearance to total elimination and the effect of renal insufficiency in patients considered to have "Wild-type"

		enzyme/protein activity, make extrapolations possible of the worst-case consequences of an impaired renal function in patients with certain polymorphisms. Similar estimations can be made for other scenarios. The paediatrics section has been updated to include the age groups specified by age.

Table 3: **MSD**

GENERAL COMMENTS		
This is a well written paper that represents a comprehensive review of the places where Pharmacogenetics could be useful. MSD suggest consideration of the following points for the development of this paper:		
Line no. + paragraph no.	**Comment and Rationale**	**Outcome**
1.	In its current form, the paper does not differentiate well the difference between compounds with broad and narrow therapeutic windows, between compounds that are specific substrates of an enzyme versus acting as inhibitor or inducer, and between compounds for which the polymorphic pathway is a sole or major pathway versus one of many parallel pathways.	The issue on broad and narrow therapeutic range is taken care of in the document when discussing clinical consequences (section 6). The consequences should be addressed with clinical data on efficacy and/or safety, obtained through direct studies at the drug exposure obtained in patients with the polymorphic alleles(s) and/or data from clinical studies where the population has been genotyped. The first set of data is also the data used when labelling a drug as having "broad therapeutic window" in this context why no change of the text is considered to be needed. We agree that the effect of inducers and inhibitors depend on the pharmacogenetic features of the protein involved. In fact, this is already indicated in section 7 third paragraph for inducers. Section 7 has been slightly revised for this to be clarified. The last issue on the importance of the affected pathway has been clarified in section 3
2.	Implementation of pharmacogenetic analyses during general drug development will be resource intensive and requires scientific knowledge that, for all metabolic pathways, may not yet be generally available. There should be acknowledgement within this guidance that for many compounds, pharmacogenetic analysis may be of questionable therapeutic value for a variety of reasons including a lack of in-depth understanding of the functional and clinical significance of many genetic variants. It should also be emphasized that this guidance is most relevant for those compounds that have relatively narrow therapeutic index AND a predictable pharmacogenetic component relative to its disposition.	We agree that the scenario mentioned will be a scenario where the clinical significance of genetic variability is large. This has been clarified in the document.

3.	The paper does not address ethical issues e.g., banking samples from early in clinical development. If this is addressed in the EMEA guidance on pharmacogenomic sampling and handling (EMEA/CHMP/201914) then consider cross referencing within the present guidance.	*This cross-reference to* Reflection paper on pharmacogenomic samples and data handling (EMEA/CHMP/201914) *is already included in section 1*
4.	The paper states that genotyping assays should be done in validated sites, but this may be limited by the practicality of academic institutions being at the cutting edge of probing new alleles. Define a "validated site" and the process by which a site would become validated.	It is yet not possible to define validated sites. However, the analyses should be done in appropriate laboratories for this purpose utilizing relevant and accurate technology and the results from the labin question should be continuously validated utilizing relevant standard samples.
5.	The paper suggests that studies should be statistically powered to study rare alleles, but does not discuss the practicality of identifying such subjects for rare alleles nor does it address that a "rare" allele in one ethnic population may be a "common" allele in another ethnic population. There is clinical value to identifying genotype/phenotype relationships in a less than statistically significant approach as a start to identifying pharmacogenetic issues that might require further study.	We agree. There may be difficulties in identifying persons carrying rare alleles and although the number found is low, the information may still be very useful if the consequences of the polymorphism affect the PK of the drug to a large extent. We added the following text to section5*: "It is acknowledged that stratification by genotype is difficult for very rare genetic variants but in many cases the effect of a particular rare genetic variant could be large and influences the specific treatment substantially."*
6.	The paper does not sufficiently guide the Sponsor to adequately define the genetic determinants to be evaluated. For example, the Sponsor may choose to evaluate a specific SNP that is known to cause a functionally significant amino acid change, but by focusing on only that SNP, may be discounting additional genetic variants within that locus that may also be functionally significant. In general, the academic pharmacogenetic community agrees that whenever possible, alleles should be defined as genomic haplotypes (within the gene of interest) that are determined by permutations of often several common genetic variations.	We agree per definition. However the document emphasizes cases where genetic variation influences the PK to clinically relevant states and such variation is mainly dependent on the presence of specific functional SNPs or CNVs(Copy Number Variations) affecting the rate of drug elimination to a large extent. This makes the relationship directly valid since the functional genetic variation is studied. By contrast, haplotypes are difficult to define because of the occurrence of many SNPs within the gene in question and the haploptype defined is often just associated to the altered phenotype.

		Thus in many cases the important mutations within the haplotype defined have not been identified, making the conclusions more difficult to make.
7.	It would be helpful if the guidance were to give practical examples when possible. For example, when describing in Section 3 that PG should be evaluated for correlation with PK variability – describe and cite literature for some of the many examples of, for example, CYP2D6 poor metabolism and altered pharmacokinetics of drugs. In general, for each situation in which the Paper suggests implementation of PG analysis, a "real life" example should be provided with citation of pertinent literature. This is important because the pharmaceutical industry is not accustomed to doing PG studies whereas there are many examples in the published literature that speak to the functional significance of metabolic pathways relative to specific drugs. Also, the paper should direct the reader to a body of review literature on pharmacogenetics.	The document is provided as guidance but not a literature review. However, relevant literature can be obtained form the public domain.

SPECIFIC COMMENTS

SECTION 1 **Introduction**

Line no. + paragraph no.	**Comment and Rationale**	**Outcome**
Para 1	The list of drug metabolizing pathways is not complete. Much is understood about genetic variation in metabolism pathways other than the CYPs. Perhaps a more complete list of metabolic pathways (including reference to specific UGTs, NATs, Methyltransferases (MTs) and sulfotransferases (SULTs) is warranted.	These enzyme families are already included in the text of this subsection. No further mentioning is needed.
Para 1, Line 8	It might be wise to avoid assigning "importance" to specific drug metabolizing pathways (i.e., CYP2D6, CYP2C19 and CYP2C9). Many drug metabolizing pathways are polymorphic and for drugs that are metabolized entirely by, for example, Thiopurine Methyltransferase (TPMT), that enzyme is more "important" than any of the CYPs. There are numerous examples of genetic variants in genes other than CYPs that are highly clinically "important".	We agree that it is unnecessary stating which polymorphisms are most important. We have therefore replaced "are" by "include".

SECTION 2 **Scope**		
Line no. + paragraph no.	**Comment and Rationale**	**Outcome**
	This paper seems to define Pharmacogenetics only with respect to drug metabolizing pathways. There is a history of confusion with regard to the definition of "pharmacogenetics" vs "pharmacogenomics". It might be helpful to clearly state that this paper addresses only drug metabolism pathways and acknowledge that drug disposition can also be affects by genetic variation in transporters and in drug targets.	Little is known at present regarding the in vivo importance of genetic differences in transporters, therefore focus is put on enzymes. However, the paper includes both transporters and enzymes, and this is indicated e.g. in section 1, 1st paragraph: "*The additional contribution of polymorphism in drug transporter has recently been recognised*". In the remainder of the paper, transporters are indicated where considered relevant. The sentence asked for appears already to be in the document (section 2). "*The broader issue of pharmacogenomics (PGx), i.e. the variability in the entire genome relevant to drug response, will not be considered in this reflection paper.*"

SECTION 3 **In Which Situations should the effects of PG on PK be studied**		
Line no. + paragraph no.	**Comment and Rationale**	**Outcome**
Para 1, Line 1	The first sentence of this section states that PG studies are required if "polymorphically expressed proteins are known to be involved…". This statement might be better worded as "if genetic variation in proteins known to be involved in major pathways of metabolism or transport….". It is a little dangerous to use the terminology "polymorphically expressed" since some functionally significant genetic variants affect the expression of the protein and some do not.	We agree and have changed the text in accordance with the proposal.
Para 2, Line	It is stated that PG studies should be undertaken in "compounds (that) exhibits important interindividual PK variability." This may not be cost-effective nor therapeutically warranted	This is specified in the last part of the sentence, i.e. "…*potentially affecting clinical efficacy and/or*

2	if there exists a wide therapeutic window.	*safety*".
Para 2, Line 8	It is stated that when unsure of the pharmacogenetic target "(samples) should be collected for further analysis." This may be ethically challenging in some countries.	To the opinion of the EMEA PGWP, collection and storage of these samples is considered important, both for testing of PK related genes as well as genes related to efficacy and safety.
Para 3, Line 1	It is stated that "for authorized medicinal products, PG/PK studies may be still valuable when new populations" are investigated. This is useful, but many currently marketed compounds should also be studied when new knowledge or technology is available regardless of if they are introduced in new populations.	We agree completely but this kind of studies can presently not be formally requested by the agencies unless the risk-benefit is negative for the whole target population.
Para 2, Line 3	A statement is made that "Technology has advanced to the point that analysis of genetic factors affecting safety and efficacy of medicines is now fast and reliable". While this may be true when considering the throughput and cost of genotyping, it does not solve the continued problem of knowing the functional significance of genetic polymorphisms. This field has not yet established which alleles are truly functionally or, harder yet to understand, clinically significant for many drug metabolizing pathways.	It is correct that there is a lack of knowledge regarding the true functionally important SNPs in many genes that affect PK. However, it can be anticipated that a majority of the detrimental mutations in genes encoding drug metabolising enzymes affecting PK have been identified. The issue of application of pharmacogenetics today is mainly concerned around such polymorphisms.

SECTION 4 **At what state in the clinical development program should PG/PK studies be preformed**		
Line no. + paragraph no.	**Comment and Rationale**	**Outcome**
Para 1, Line 6	States that if in vitro data shows possible PG importance, "inclusion of genotyping directed to the candidate gene in early phase I studies is warranted." It should be acknowledged that for rare alleles, such hypotheses may not be testable until larger study populations are targeted. It should also be stated that when a narrow therapeutic window exists or is suspected, careful dose selection should be considered for sub-populations with different genotypes.	We agree that directed studies of subjects with different genotypes may be difficult in case the allele frequency is too low. However, even in this case, genotyping could still be performed for information to be gained at that stage and in future analysis of the whole PK population studied. The choice of dose for PMs will depend of the therapeutic window. This is not usually included in guidelines but should be carefully considered by the investigator in all PK

		studies where a clinically relevant increased exposure is expected. Although agreed on, the sentence will not be included in this guideline.
Para 2, line 1	States that PG/PK studies should be performed with compounds that have "unexplainable PK observations." This is really only warranted for compounds with a known or suspected narrow therapeutic window relative the PK variability.	We agree that these studies are not needed if the difference in drug exposure is not clinically relevant. The text has been slightly changed for clarification.
	Sponsors should be encouraged to identify populations that may be enriched with alleles of interest especially if the allele in question is of rare frequency in many populations.	We would indeed support applicants to identify populations that may be enriched with alleles of interest especially if the allele in question is of rare frequency in many populations. This has been included in section 8.

SECTION 5 **Study design and methodology**		
Line no. + paragraph no.	**Comment and Rationale**	**Outcome**
Para 1, Line 4	It is stated that "the study should include a satisfactory number of patients of each genotype." This may be difficult especially when several alleles (some of which are rare) contribute to a variant phenotype. Consider CYP2D6 in which several alleles and ethnically-specific alleles contribute to the “poor metabolizer” phenotype. In such cases, it may be more beneficial to study a surrogate phenotype rather than genotype.	Phenotyping could in many cases be of value. In fact genotyping can never completely predict the phenotype due to the presence of e.g. nonidentified SNPs. At the same time phenotyping can lead to erroneous conclusions due to drug interactions, impaired organ function etc. However, what is meant is that enough number of patients having variant alleles translating into a specific phenotype with respect to the drug PK should be taken into consideration in the study.
Para 2, Line 1	States "the genotyping methods should first be validated and maintained under continuous quality control." For very rare alleles e.g., CYP2D6 the polymorphisms might recently be discovered and genotyping may only be available at sites that do not meet these standards.	We are aware of that validation of genotyping methods for very rare alleles are difficult using standards. In these cases it would be sufficient to make careful sequence analyses as a validation of the genotyping method used.

	The terminology used in this section should be revised to avoid the use of the word "mutation". In some clinical circles, "mutation" confers a meaning of disease-causing while in the pharmacogenetic community this word usually means occurring at a frequency of less than 1%.	We have changed the term "mutations/alteration" to "variations/alterations".

SECTION 6 **Evaluation of the clinical consequences of genetic differences in drug substance exposure**		
Line no. + paragraph no.	**Comment and Rationale**	**Outcome**
Para 3, last sentence	Please define "SPC".	This has been added.

SECTION 7 **Special considerations related to drug-drug interactions and impaired or immature organ functions**		
Line no. + paragraph no.	**Comment and Rationale**	**Outcome**
	This section discusses need for drug interaction studies. Currently, there are many possible interaction studies for major drug metabolizing enzymes. However, this is not standardized across industry. More guidance and standardization would make these results more readily interpreted.	We do not fully understand this comment. There is a guideline on this matter (CPMP/EWP/560/95). Although a bit old, its contents are still generally valid. This guideline is cross-referred to in section 1.
Para 5	This sections recommends the study in special populations with impaired or immature organ function e.g., children. It is important to recognize that age differences (particularly regarding neonates) might mask PG interactions. Ontogeny of drug metabolizing enzymes is an emerging body of knowledge that suggests that drugs may be metabolized differently in the very young or very old populations. The relevance of specific variants in those populations to other populations may not be clear.	We agree that the text was not completely clear and have added further information. As stated, there may be differences in metabolism between children, especially between very young children, and adults. Therefore, the impact of PG differences may be different in young children and adults. This is further discussed in the guideline "Guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population (EMEA/CHMP/EWP/147013/2004)"

	When regarding drug-drug interactions, it is important to acknowledge that for individuals with a genotype that would predict an "intermediate" phenotype, a drug interaction might be much more clinically meaningful than in an individuals with an "extensive" phenotype. This phenomenon is illustrated with the example of olsalazine (Dipentum), an inhibitor of TPMT. Osalazine is often co-administered with thiopurine drugs (that are metabolized via TPMT) in the treatment of inflammatory bowel disease. It is now recognized that patients who have an "intermediate" phenotype for TPMT are at risk of life threatening drug-drug interactions when co-administered olsalazine and thiopurines, an interaction not manifested clinically in patients who are "extensive" TPMT metabolizers.	We agree and have included some recommendations on this. The following text was added: "*The consequences of inhibition of a protein in a population with a lower but not abolished activity of that protein should also be considered.*"

SECTION 8 **Treatment recommendations based on genetically determined differences in exposure.**		
Line no. + paragraph no.	**Comment and Rationale**	**Outcome**
Para 2	This section recommends that dose titration can be made by Therapeutic Drug Monitoring (TDM) without qualifications. This approach is most needed when drugs have a narrow therapeutic window or specific dosing targets are needed e.g., antibiotic MIC.	We do not understand the wording "without qualifications". A target concentration range must be available if TDM is to be used in this context. The section starts "*If there is a need for dose-adjustment…*" This shows that normalisation of exposure is not requested unless there is a clinical reason to do so.
Para 3	This section also recommends the possibility of dosing with respect to genotype or phenotype. Currently, most patients are neither genotyped nor phenotyped in the routine clinical setting. Thus, a further explanation of the logistics of this is needed.	If there is a need to genotype the patients prior to starting therapy and no other actions are suitable, the prescriber can either perform genotyping or chose another drug. Hopefully, the access to genotyping analysis will be adjusted to the clinical need.

Table 4 **TEDDY**

GENERAL COMMENTS - OVERVIEW
The document focuses on the role of PGx as causal factor to variability in drug exposure, and in particular in drug metabolism. However, little discrimination is made between the impact of genotypical vs phenotypical differences and the need to establish the level of a genetic effect or interaction, i.e., how different expression patterns alter protein and enzymatic activity. Such a restricted focus precludes the reader from assessing the contribution of other relevant factors, which equally or primarily determine drug exposure or are confounders and cannot be ignored in any sound statistical analysis. *Outcome: In the pharmacokinetic evaluation, the effects of different internal and external factors are evaluated. PG is one of these and this guideline specifically focuses on this aspect.*

SPECIFIC COMMENTS ON TEXT		
SECTION 3 **In which situations should the effect of PG on PK be studied**		
Line no. + paragraph no.	**Comment and Rationale**	**Outcome**
	Assessment of Causality between variability and PGx factors The proposal as such may lead to identification of non-causal correlations between genetic polymorphisms and variability in drug exposure. It also underestimates the need to understand whether genotypical or phenotypical differences are clinically relevant. The document does not provide enough information on how one should evaluate these aspects. Most importantly, it would benefit from further considerations on the dynamics of the phenotype and its link to the genotype by an integrated model-based approach. Multiple testing and ad hoc statistical analyses are common practice in genetic research. Appropriate methodology for multivariate analysis, including nonlinear mixed effects modelling and Bayesian hierarchical modelling must be considered as primary methodology.	There are many potential statistical methods to use like the ANOVA, t-test, Fisher exact, Wald test, Mann-Whitney, Kruskal-Wallis etc, but the use is dependent on the settings applied for the study and no general recommendations can be done.

SECTION 7. **Special considerations related to drug-drug interactions and impaired or immature organ functions**		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	Role of developmental changes Many of the disease processes affecting newborn infants (e.g. congenital infections) and diseases of childhood (e.g. Kawasaki's disease) have no adult correlates. Similarly, acute lymphoblastic leukaemia, Wilm's tumour and neuroblastoma are all mainly encountered during childhood, and rarely (if at all) in adults. New models and methodology are therefore needed to assess relevant pharmacokinetic and pharmacodynamic parameters (e.g. clearance, bioavailability) taking into account their time-dependencies. The results of ontogenetic and pharmacogenomics research should be used to elucidate the developmental events that affect diseases and drug treatment response in children.	We agree that effects of certain polymorphisms in very young children also depend on ontogenetic factors. This is also discussed in Guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population (EMEA/CHMP/EWP/147013/2004)

SECTION 3**. In which situations should the effect of PG on PK be studied**		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	Definition and relevance of polymorphisms Throughout the paper the word polymorphism is repeated but we must we must remind what a polymorphism is, i.e. a term of epidemiology, indicating an allele with a frequency in the population higher than 1% (some experts suggest 2%). Thus a polymorphism could be with or without phenotypical relevance (silent polymorphism). To have a phenotypical effect, the polymorphism must be one in the critical SNP for the expression of the gene (promoter, enhancer, coding sequence, introns). The phenotypical effect must be an increase or reduction in structure and expression of the protein. But we must underline that there are at least two additive mechanisms that affect protein expression: one is methylation of the promoter (the same of acetylation) and the second is destroy machinery of the proteins (ubiquitination).	In section 8 we added the following text covering ethnic genetic differences: "*The frequencies of the alleles of interest in different populations, especially if the allele in question is rare in many populations, should briefly be presented in the SPC.*" See also response to first specific comment by Bristol-Myers Squibb.

	So, one must be careful in not overestimating the clinical and biological relevance of a polymorphism. As a consequence, we believe that most polymorphisms will not have a clinical relevance. In conclusion when you have to plan for a new drug you must be aware of the drug metabolism and of all the proteins involved in it. Studies on the presence and the localization of all the polymorphic sequences in the genes codifying for these proteins should be planned as well as studies in a cellular model in order to investigate the significance of these polymorphisms. Only for the clinically relevance you have to study a population to verify the allele frequency. Regarding this latter you must be aware that different ethnic populations have different allelic frequencies.	

SECTION 8 **Treatment recommendations based on genetically determined differences in exposure**		
Line no. + para no.	**Comment and Rationale**	**Outcome**
	Labelling and dosing recommendations The proposed strategy on how pharmacogenetics may contribute to the selection of the patient population and /or dosing regimen and possible titration is in principle valid. However, as indicated above, it overestimates the role of the pharmacogenetic factors. An integrated approach that incorporates all relevant determinants of drug exposure and response is mandatory for accurate decision making and clinical recommendations regarding efficacy and safety.	We agree upon that several different factors have to be considered regarding dose regimen etc. We are however not of the opinion that there is an overestimation of the impact of PG. The section starts with “If there is a need for a dose adjustment,”. This route is taken for the impact of other factors as well such as age, organ function and interactions.

Table 5: **Department of Biochemistry and Medical Biotechnologies University Federico II of Naples, CEINGE- Advanced Biotechnologies, Naples- Italy**

GENERAL COMMENTS - OVERVIEW
I read carefully the manuscript on pharmacogenetics of EMEA commission of July 2006 on Pharmacogenetics. It is a very well done work. Anyway I want to underline one point: In all the paper there is the word polymorphism and I believe that we must remind what a polymorphism is: is a tern of epidemiology, it indicates an allele with a frequency in the population higher then 1% (2% for the authors). So a polymorphism could be with or without phenotypic relevance (silent polymorphism). To have a phenotypic effect the polymorphism must be in one of the critical area for the expression of the gene (promoter, enhancer, coding sequence, introns). The phenotypic effect musty be an enhanced, or a reduced or a structural variant of the protein. But we must underline that there are at least two additive mechanisms that affect protein expression: one is methylation of the promoter (the same of acetylation) and the second is destroy machinery of the proteins (ubiquitination). So we must be careful because not all the polymorphisms have a phenotypic significance. Second the phenotypic effect, in may opinion, only very rare causes a phenotypic effect. In conclusion when you have to plan for a new drug you must be aware of the metabolism of this and of all the proteins involved in this. Study in public data the presence and the localization of all the polymorphic sequences in the genes codifying for these proteins. Study in a cellular model the significance of these polymorphisms Only for the clinically relevant you have to study a population to verify the allele frequency Regarding this latter you must be aware that different ethnic populations have different allelic frequencies. *Outcome: See above (Comments from TEDDY Network of Excellence)*

Table 6: **Schering-Plough**

GENERAL COMMENTS
Schering-Plough agrees with the overall intent of this reflection paper which is to better define how pharmacogenetics should be used during clinical drug development.

SPECIFIC COMMENTS ON TEXT		
SECTION 4 **At what stage in the clinical development program should PG/PK studies be performed.**		
Section no. + paragraph no.	**Comment and Rationale**	**Outcome**
S 3 PG 2	The document states that "In all cases where unexplained PK variation has been identified, samples for pharmacogenetics purpose in further clinical trials, should be collected for future analysis." We agree that this is true, and currently put forward great effort to ensure that this is done. A difficulty we face as we attempt to prospectively collect samples for future analysis is the hurdle of getting this approved in many countries globally, including some in the EU. Proposed change: It would be helpful to emphasize the importance of allowing companies to collect genetic samples for future analysis- especially allowing these samples to be stored at a minimum through the entire regulatory review process.	We acknowledge your concerns and would like to emphasise that this is important; both for testing of PK related genes as well as genes related to efficacy and safety. However, this important aspect is not the purpose of the document.
S 4 PG 1	*In vitro* techniques for predicting the relative contribution of common, well characterized enzymes are routinely included during preclinical development. They have provided a valuable tool for predicting the most common enzymes involved in Phase I drug metabolism and this information is known prior to first-in-human studies. However, determination of the relevant Phase II isozymes or transporters involved in disposition of NMEs are not (in all cases) robust and are therefore not routinely done. Proposed change: Please comment on the importance of genetic sample banking in order to conduct retrospective exploratory analyses for PG/PK relationships that are not currently predicted by *in vitro* studies.	We agree and have added text accordingly. See above.

SECTION 5 **Study design and methodology**		
Section no. + paragraph no.	**Comment and Rationale**	**Outcome**
S4 PG 3	Genotyping during Phase I, II, III clinical studies to support dosing recommendations for genetic subpopulations is an exciting opportunity. It should be noted that there is a limitation for quantifying dosing, in many cases, for the heterozygote population, even for highly penetrant single gene polymorphism studies. It is also important to note that new PG/PK relationships will be uncovered by exploratory work that will be confirmed in larger post-marketing population studies.	We agree that defining dose-adjustments of the heterozygote population may be difficult. In general however, we consider that efforts should be made to recommend specific doses in as many relevant subpopulations as possible. Overall, we do not think this needs specific mentioning in this paper.
S5 PG 1	The statement that in a conventional PK study, the study should include a satisfactory number of patients of each genotype in order to obtain valid correlation data could require (for less frequent polymorphisms) thousands of patients to be screened. In one recent example, 3000 patients were screened to identify 12 homozygous mutant patients. <u>Proposed change:</u> The value of retrospective exploratory analyses should also be discussed. Stratification of patients by genotype is difficult for rare polymorphisms, and the feasibility of conducting these types of studies during drug development should be discussed.	We agree that it may be difficult to stratify studies for rare alleles. The text has been changed to reflect this.
S5 PG 1	Weighing the importance of inhibitor studies to determine variation in PK versus using a stratified genetic population will be a future challenge for the pharmaceutical industry. The observation that traditional PK studies designed to investigate inhibitors of metabolism is a less demonstrative approach may not always be the case. There are some well-characterized substrates/inhibitors of common DMEs that we know how to quantify in the context of a PK variability or drug interaction study. Additionally, PhRMA recently published a White Paper and the US FDA issued a guidance discussing the utility of these studies for drug-drug interaction studies. <u>Proposed change</u> It would be interesting to comment on the fact that we don't yet know, in certain instances, if enrolling enzyme deficient patients is practically better than conducting enzyme inhibitor studies because we don't yet know the limits of PG for predicting a truly "deficient" state. As data evolves in this area, this will be important to reassess.	We agree that the approach of using a very potent inhibitor may be misleading and the results may be difficult to interpret. The suggestion has now been removed.

S8	It is also interesting to consider how PG information incorporated into the label will affect the clinician's ability to use the drug and interpret efficacy/toxicity.	We await practical consequences of providing such data.

Table 7: **Czech Republic Medicinal Board**

GENERAL COMMENTS		
Further, we describe few specific comments on the reflection paper, which in our opinion wel1 reflects current status of knowledge in the field.		
Section no. + paragraph no.	**Comment and Rationale**	**Outcome**
1. Section	"Study design and methodology" last sentence of the section selectively mentions a specific type of genetic variations („copy number polymorphisms") that can be of functional significance in the pharmacogenetic field We do not consider being useful selectively adverting this not very frequent type of polymorphisms. Therefore we propose to delete the following sentence "The analysis should include methods that can identify major genetic variation such as copy number polymorphisms."	Indeed copy number variation (CNV) polymorphism contributes to the major interindividual genetic differences in nucleotide sequence between two individuals as recently evident from the Human genome project as published in Nature Genetics. In the field of pharmacogenetics it is an essential feature in that many phase I and phase II drug metabolising genes like CYP2A6, CYP2D6, SULTs and GSTs exist in copy numbers of 0, 1, 2, 3 and more in different subjects. This phenomenon translates into important phenotypic differences as described for e.g. CYP2D6. The CNVs are advantageously monitored in cases of e.g non response of certain drug therapy or ADRs. We do think this is an important aspect that has gained more attention very recently.
2. Section	5 "Study design and methodology" Paragraph ,"Conventional PK analysis and population PK analysis" a The term mutation is used for a genetic variation with allelic frequency less that 1% in the population. This leads under assumption of normal distribution of genotypes corresponding to Hardy-Weinberg equilibrium to frequency of homozygous carriers of the variant allele less than 1:10 000 in the population. Complete and/or significant deficiency of drug metabolizing enzyme or transporters is generally inherited in recessive way Therefore we suggest the	a. Agreed. We have modified the term "mutations/alterations" into "variations/alterations".

	Reflection paper should focus on polymorphisms with more frequent distribution in the population. Therefore the expression ,,mutations/alterations" should be replaced by "polymorphisms" or more generally "variations/alterations". If the terminology of "polymorphisms" were used, at least some guidance would be provided with respect to which of the large number of known alleles should be studied in target populations. b. Last sentence of the paragraph .Mimicking the absence of a functional ..." is surely a truth, but the interpretation of data obtained from an interaction study seems to be rather difficult In our opinion such a data wil1 always be only a proof of an interaction without uncovering the significance of genetically determined pharmacokinetic variations As an example can be mentioned known interaction between loperamide (substrate of P-glycoprotein) and quinidine (inhibitor of P-glycoprotein) leading to inhibition of respiratory center. Functional polymorphisms in the respective gene fortunately do not result in this serious clinical consequence. Moreover interaction potential in subjects of different genotypes may substantially vary. Therefore we propose to delete this sentence.	b. We agree. The suggestion to use inhibitors has been removed.
3. Section	5 "Study design and methodology" completely lacks the possibility of using phenotyping, while the sections related to SPC permit to use phenotype-based precautions. As phenotyping can in specific situations bring some advantages over genotyping we propose to add this method also into the section 5.	Phenotyping could in many cases be of value. In fact genotyping can never to 100 % accuracy predict the phenotype due to the presence of nonidentified SNPs. At the same time phenotyping can lead to erroneous conclusions due to drug interactions, impaired organ function etc. However, what is meant is that enough number of patients having variant alleles translating into a specific phenotype with respect to the drug PK should be taken into consideration in the study. The guideline has been changed to reflect this point.

Table 7: **EFPIA/Contact Person: Christine-Lise Julou**

GENERAL COMMENTS
EFPIA appreciates the opportunity to comment on this reflection paper. We recognise the importance of initiating considerations on pharmacogenetics (defined as PG in the paper and used herein) specifically applied to pharmacokinetics (PK) to develop new medicines. In the specific context of building evidence for the adequate assessment of safety and effectiveness of a new medicine, there is general agreement among the EFPIA companies that this reflection paper is produced at an appropriate time. As acknowledged in the paper, metabolism and transport mechanism of drugs are now well recognised to be influenced by genetic polymorphisms or variations. Since PG has entered drug research and development, the emerging capabilities based on the genome methodologies, make the paper relevant and timely to initiate thoughts, share common understandings and identify gaps in those understandings. It is important to recognise that many of the concepts and clinical applications of PG on drug PK are still evolving and require further examination. With this in mind, a concern of EFPIA is that much of the wording contained in the present reflection paper appears to suggest that these PG concepts are fully established in PK, perhaps even to the level of working practices which are well-validated, and straightforward to conduct (e.g. "fast and reliable"). **Instead, the role of PG on drug PK is still an area where much needs to be understood in the context of the drug development process.** Thus rather than an end goal, PG is a means to the end, so that based on accumulating data and the PK strategy specific to each drug, PG **may** be indicated as an additional tool in PK investigations in drug development. **Thus, any prescriptive or definitive recommendations as stated in the paper are premature.** *Outcome:* *In a drug development program, the impact of PG on PK and efficacy/safety should be investigated if the effect of polymorphism on the PK is likely to be of clinical importance. If marked changes in drug exposure are found, the impact on safety (and/or efficacy) should be investigated or supported by clinical safety data on the obtained exposure. The results should then be translated into treatment recommendations. What kind of recommendation found satisfactory is dependent on the consequences of having a deviating genotype and the possibilities to adjust (titrate) the dose based on other clinical markers. We find no reason to remove the treatment recommendations from the document. The scenarios where the different options would be suitable are included as guidance.* Given that PK studies in developing new medicines are generally not powered to detect PG effects, initial PK/PG association analysis should be considered exploratory. Sponsors should be encouraged to collect samples and generate data if required, throughout clinical development of a drug and place PG approaches in this context. As the level of confidence in specific PK/PG interactions increases (based on emerging evidence), then specific, appropriately designed and powered studies to test PG hypotheses may be incorporated into the development program. *Outcome:* *We agree that the conventional first phase I studies most likely will be too small to result in anything but indications of marked PG/PK effects. However, if there are indications of a marked effect on PK based on in vitro data, published scientific literature and other available data, a directed study to evaluate PG effects on PK should be made as early as possible in the clinical development program. Such data could then be reflected in further clinical studies (eg exposure-response studies) as well as further monitoring incl. genotyping in the Phase I, II and III studies. The scenario in which it is suspected that PG is the cause of inter individual variability in PK observed, we agree that PG/PK studies could be performed later in the development program.*

The latter sections of the paper seem to reflect a certain expectation that PG-based dose determination will be the rule, rather than the exception. EFPIA expects the opposite – that requirements to base dosing on PG will not be required for the majority of medicines, and that --while information about relationships between genotype and PK may become more common in SPCs,-- the majority will continue to be approved for clinical use without PK/PG language or mandating of a PG test in the SPCs (unless there is sufficient scientific basis and data for doing so).

Outcome:
It is possible that the number of drugs with mandatory PG based dosing will be small. Future will show the importance of PG based dose-recommendation. The aim of the document is not to recommend PG based dosing of drugs for which this is not needed. The document presents the data needed to evaluate the impact on PG on PK, safety (and efficacy) as well as possible ways to translate a PG effect into treatment recommendations.

In summary, EFPIA has given substantial consideration to respond to this paper. Rather than a comment 'line by line' on proposals in the reflection paper the EFPIA response is structured as follows:

a) Key Themes: These represent major topics in which EFPIA believes the current reflection paper could be augmented or where it diverges from key focus of PK and/or PG as they pertain to drug development.

b) Section Table: Major comments are itemised according to the section numbers of the original reflection paper (but not to a specific line or word, unless a 'key theme' as defined above).

c) Future Workshop: Given the rapidly emerging and multidisciplinary nature of PG in PK, and the regulators desire for a reflection paper EFPIA proposes a focused and interactive workshop. Ideally this would be prior to the next EMEA document on PG/PK and involve key stakeholders to permit more in-depth dialogue and exchange of learnings with experts in the drug development applications of PG and PK. Examples of key stakeholders would include regulators (national/EMEA), industry, and medical practitioners.

(a) *KEY THEMES:*		
Section no. + paragraph no.	**Comment and Rationale**	**Outcome**
1.	**Differentiate PK in drug development from medical practice and/or academic research.** The expectations for regulators, scope for readers, and subsequent questions should be clearly aimed at **drug development**. Thus the objective needs to be on assembling PG evidence which **may** improve the safety and efficacy of a new medicine and in a context which typically is a controlled study - in this case, PK clinical trials -.	The document is indeed aimed at drug development and use. Studies which are not mandatory and only recommended are clearly distinguished from the requested studies.
2.	**Position the PG influences on PK into context with all other emerging evidence and the PK design strategy specific for each drug.** There is agreement with the overall philosophy that genotyping should be performed where there is a specific hypothesis or development need, and that any genotyping should be data driven, e.g., by existing *in-vitro* or *in-vivo* data, unexplained variability, potential formation of toxic metabolites, speculated route of metabolism, etc. We agree that PG sampling and analyses should be implemented early in the development process and that, in general, should be an integrated part of clinical development programs since this allows both for existing hypotheses to be evaluated and for emerging clinical issues to be addressed. Thus PG is a component of PK variation but not the sole factor.	We agree and find it quite obvious that other internal as well as also external factors can influence PK and that the effect of these factors should be investigated in accordance with the available guidelines. We do not think that this has to be further clarified.

3.	**Given that PK/PG interactions are presently at an exploratory and hypothesis-generating stage, avoid any substantial departures from current practice (for example, in Sections 3, 7, 8).** Currently there are few clear examples whereby the role of PG in PK variation and its potential clinical utility has been established and it is important that expectations reflect the early stage of the science. It is suggested that text in the paper like "should be", "require", "warrant" or proposals for SPCs are removed. Recommend: EFPIA suggests that certain sections are reworded following interactive exchanges via workshops and/or ad hoc multidisciplinary roundtables on PK/PG studies relevant to clinical drug development	Presently, there are few cases where PG based dosing is recommended. This is probably due to the following reasons: a) a PG effect can often be solved by dose titration (eg warfarin) b) a drug where the consequences of being a PM is severe may not be approved c) a drug where the consequences of being a PM is moderate to severe could have a positive risk-benefit in the whole population and might have been approved without genotyping recommendation due to the limited access to PG analysis. d) there was little of no available data on PG effects on PK at the time of drug approval As you state earlier, PG is one of many factors which may markedly affect the PK, efficacy and safety of a drug. If the effects of PG have clear clinical relevance, we see no reason not to translate the effect into treatment recommendations either as mandatory or optional genotyping or as dose titration suitable also for he genetically deviating patient group.

4.	**Recognise that PK studies in drug development are not usually powered to detect PG effects in sub-populations** If references to power are included in this paper, then it is important to be explicit or clarify the specific drug development question being addressed and the likely 'generalisability' or limitation of the PG data generated.	The conventional PK study could be stratified for the most common genetic subgroups or with subjects selected from panels with known genotypes. The power of a clinical study to detect a difference in e.g. clinical safety will depend on the frequency of patients with a specific genotype as well as the magnitude of the effect. Here, exposure/dose – safety studies covering the exposure obtained in genetically deviating patients can provide useful supportive safety data.

(b) ***GUIDELINE SECTION***

SECTION 1 **Introduction**

Section no. + paragraph no.:	**Comment and Rationale**	**Outcome**
1.	As this section sets the expectations for the rest of the paper, it is notable that extensive detail is given to CYPs and metabolism. Thus the current reflection paper tends to reflect what has been most extensively studied, rather than what will ultimately turn out to be the most important for PG in drug development. As variation in PK also involves other components of drug absorption and disposition (distribution, metabolism, excretion), we would suggest that this needs to be mentioned at this point. The following text "**a good deal of this variability results from genetic polymorphism"** should be reworded to take into account other factors including patients' compliance, prescribing patterns, disease state or progression, diet, or even solubility of early formulations which may have a significant impact on inter-individual PK variability.	We agree and have changed the text slightly in the Introduction.
	<u>Recommend:</u> ▪ It is important to highlight that this paper does not cover medical practice (i.e. currently approved drugs) nor academic research, but drug development thereby better defining the scope in the next section, as well as answers to Questions pertaining to clinical development	This reflection paper covers drug development and further studies during a products lifecycle. This has now been further clarified.

	▪ Given that readers of this paper are likely to be from diverse backgrounds, the introduction needs to include that along with the most studied CYPs/metabolism examples, there are other ADME pathways with genetic variation that have the potential to influence PK. ▪ Also PG needs to be put into context with consideration being given to both PK **and** pharmacodynamics (PD). PD is a critical (and some might suggest more important) parameter to guide future key considerations, for example, on dose ranging and dose selection that is when PG is indicated by the evidence and specific PK strategy for each drug. The following wording is suggested: "Although less well studied, PG may alter pharmacodynamic relationships. This important area is not considered in this paper". ▪ The following text is suggested: *'Among the many factors contributing to PK variability, such as environment, disease state or progression, diet, or even formulation characteristics, genetic polymorphisms play an important role.'* and supporting reference: Andersson T, Flockhart DA, Goldstein DB, Huang SM, Kroetz DL, Milos PM, Ratain MJ and Thummel K. 2005. Drug-metabolizing enzymes: Evidence for clinical utility of pharmacogenomics tests. Clin Pharmacol Ther 78: 559-581.	Absorption was not included in the document and this has now been changed in section 3. We acknowledge that other factors exist which may contribute to variability in PK of a medicinal product. However, this reflection paper specifically focuses on pharmacogenetics being one of the possibly contributing factors. In order to maintain focus in this reflection paper, we prefer not to specifically mention other, well-known, additional causes for variability.

SECTION 2 **Scope**

Section no. + paragraph no.:	**Comment and Rationale**	**Outcome**
2.	The body of the document (appropriately) talks about how to incorporate PG/PK analysis into the existing clinical development program rather than adding specific PG/PK studies into a development plan.	The document includes both specific PG/PK studies and integrating PG into the clinical studies.

SECTION 3 **In which situations should the effect of PG on PK be studied?**

Section no. + paragraph no.:	**Comment and Rationale**	**Outcome**
3.	The last three paragraphs of Section 3 appropriately encourage utilisation of PK/PG analysis as a tool to understand inter-patient variability of exposure, efficacy, and safety, in ways that have solid theoretical bases but that have not been frequently applied to date in drug development. Apart from the obvious gene candidates possibly associated with inter-	We agree that knowledge is presently lacking in this area. Therefore we have stated that such studies are encouraged and not required. We also state that the studies are encouraged if there are indications from

	individual PK variability, it is difficult to extend the search for additional polymorphic loci in phase I studies due to small sample size and statistical issues. We would suggest that this section be modified to recognise such limitations on genetic analysis, as compared to larger, later phase studies. As an example, the original paragraph on transporters is given, as follows: **"Studies of PG differences in the activity and expression of transport proteins involved in drug distribution (efflux or influx) to target organs such as the central nervous system, possibly explaining adverse events or lack of therapeutic effect, is encouraged if there are indications of clinically important differences in these respects and a biologically relevant polymorphism is studied using cohorts large enough to provide power to make appropriate conclusions"** This paragraph suggests that genetic variants of transporter genes significantly account for variability in drug distribution. While agreed that it should be of interest as a research topic, much of the data that support this hypothesis are anecdotal and several findings have not been widely replicated. This lack of evidence concerning the pharmacological effects of most transporter variants, coupled with the lack of specific probes for most transporters to assess consequences *in vivo*, will make it difficult to conclude that a given transporter polymorphism is in fact *responsible* for a clinical outcome, even if a genetic association is observed in the context of a clinical trial. Therefore, it may not be appropriate to include a definitive statement in a document of this nature (regulatory reflection paper). Recommend: ▪ That this section be reworded to reflect EFPIA Key Themes 2 and 3. ▪ Provide working definitions for terms, some examples include: o "**PG studies**" - It is unclear if this term means that PG should be considered as a co-factor that is part of compound development (seems to be the case in other parts of the document and we assume this is the intention), or does the paper refer to PG-directed clinical trials, with PG as a primary objective? The second interpretation would not apply to most of drug development studies that include PK and PG	the clinical safety/efficacy data (and possibly from published literature) that genetic variation in transporter activity/expression may give rise to clinically important differences. We have changed PG into PG/PK in order to indicate that PG indeed should be considered a co-factor in such studies. o **"expression"** is unclear and possibly inappropriate in this context since the stated focus of the document is on genetics and not on gene expression which is not discussed in the remainder of the reflection paper. Also PG-related differences in gene expression, possibly adding variability to PK are considered relevant for this reflection paper. No change needed o "biologically relevant polymorphisms" The term 'biologically' was removed.

SECTION 4 **At what stage in the clinical development program should PG/PK studies be performed**		
Section no. + paragraph no.:	**Comment and Rationale**	**Outcome**
4.	As our understanding of the true impact of PG on PK variability is still evolving we believe that the use of terms such as "**major involvement",** "**known to be subject to", "verified", "markedly affect", "contributing**", "**warranted**" are premature and ultimately require agreement on their usage and qualification. These basically all refer to the future application or eventual product profile resulting from application of the PG marker i.e. its positive predictive value (PPV) and negative predictive value (NPV), and will differ on a case-by-case basis. For example: a) *In vitro* data may not always translate quantitatively to the *in vivo* context and minor routes of metabolism may also be important. Consider the classical example of codeine metabolised to the active moiety, morphine, via CYP2D6; less than 10% of administered codeine is metabolised this way and not considered "major involvement" in an *in vitro* assay. However, therapeutic efficacy of codeine is well known to be largely due to the metaboliser status of CYP2D6. b) Tools such as those readily available for CYPs are unavailable for expressed enzymes and functional transporters. Further, prior to clinical development, there is no information on the fraction of human clearance related to drug metabolism, including the CYPs, so PK predictions based on animal and in-vitro human studies may not translate to the clinical situation. <u>Recommend</u>: ▪ Appropriately amend language as per Key Theme 3. Text should clarify that specific PK/PG studies are warranted only when the genotype-PK relationship is established for safe and effective use of the drug and a PG test will be used in the clinic. In other words, the evidence to use PK/PG data to inform dose selection in drug development differs from that required when incorporating PG data into the SPC and hence prescribing practice. Thus PK/PG analysis integrated into usual clinical studies needs to be placed in context to all the evidence, which supports informative language in the SPC. ▪ Another example is the original text of "**In general, PG should be an integrated part of the clinical study program. Sufficient knowledge should be collected in the phase III studies to satisfactorily clarify the efficacy and safety consequences of the PG-**	We are aware that in vitro contribution not always quantitatively translates into in vivo contribution. However, the important information from the ADME study and an interaction study with a potent inhibitor quantifying enzyme contribution, is usually available late. Therefore, early genotyping in PK studies can give valuable information including early knowledge on main enzymes involved (which can be reflected in safer clinical phase II and III studies) as well as contribute to an as large data base as possible on the effects of PG on PK and safety. We agree and the text has been changed accordingly. We have modified this section to indicate that not all *drugs need PG studies. The sentences now read: "When the genotype is predicted or known to markedly affect the PK of pharmacologically active compounds contributing to in vivo efficacy and/or safety of a medicinal product, genotyping is encouraged in as many of the phase I, II and III clinical studies as possible to increase the amount of data that will support the recommendations for use in the genetic subpopulation(s).* Dose-response

	dependent PK differences." replaced by **"In general, PG should *be considered as a potentially applicable part of any clinical development program, and appropriate studies conducted, if indicated by in-vitro and/or in-vivo data, supporting information and expert knowledge".***	studies or other clinical studies covering the exposure of active substances obtained can be used to support safety and efficacy in a specific genetic subpopulation.

SECTION 5 **Study design and methodology**		
Section no. + paragraph no.:	**Comment and Rationale**	**Outcome**
5.	The more common PK/PG exploratory approach in drug development is the integration of the PG analysis (where indicated) into the standard clinical study design. These study designs often involve either sparse PK sampling or small numbers of participants which make correlation of genotype with phenotype challenging for all but the most common polymorphisms. Hence for many studies there will not necessarily be sufficient numbers of each genotype to clearly establish a relationship between genotype and PK, and power ('informativeness') calculations will only be possible post-hoc when the size of the effect and the genotype distribution is known. This situation should be the exception, rather that the rule, in drug development. If genotype were indeed felt to be a significant contributor to PK variability, and a PG test likely required for optimum dosing in the clinical setting, then it is likely that a dedicated study would be necessary for hypothesis testing (either demonstrate/exclude presence of a specific allele or genotype as a major contributor). <u>Recommend</u>: ▪ As per Key Theme 4, if reference to power is included in the paper, then it is worth specifying the purpose of power calculations prior to the initiation of the study. Are they to ensure sufficient study size or are they to be used to assess if PG analysis should even be considered? ▪ Clarify that where a PG test is going to be necessary for the safe and effective use of a new drug in clinical practice that it is likely that a specific PG/PK study will be required to clearly establish the PG/PK effect. It is unlikely that this will be required for the majority of drug programs.	We have clarified the reason for power calculations. We agree that a "conventional PK study" stratified for the most common genotypes will most often be the more advantageous approach, if it is feasible to find carriers of the polymorphic alleles and to administer the drug to healthy volunteers. If the sparse sampling population PK approach is used, the number of patients included has to be sufficient to allow detection of a clinically relevant effect. As you suggest, if it has been identified that there is a need for genotype based dosing, it is likely that a specific PG/PK study is needed to support dose recommendations unless there is sufficient data already available.

SECTION 6 **Evaluation of the clinical consequences of genetic differences in drug substance exposure**		
Section no. + paragraph no.:	**Comment and Rationale**	**Outcome**
6.	Recommend rewording as per Key Theme 3	If (and only if) there is a patient population with potentially relevant altered drug exposure, the clinical consequences should be assessed. This is already standard practice. There is nothing new in this section besides putting practice down on paper and pointing out the need for clinical data in order for this assessment – if necessary- to be possible. If a patient population deviates due to impaired organ function or an interaction to such an extent that no clinical data is available it is not uncommon for use in this patient group to be contraindicated. This situation is not satisfactory and therefore, in order to prevent this from happening, data should be available for a proper assessment to be made. This is the key message from this section. For clarity we have added "If relevant PG-related differences are present for a medicinal product," to the first sentence in order to make clear that this is applicable for medicinal products with relevant PG-related PK effects, and not generally applicable for just any medicinal product.

SECTION 7 **Special considerations related to drug-drug interactions and impaired or immature organ functions**		
Section no. + paragraph no.:	**Comment and Rationale**	**Outcome**
7.	This section highlights a range of opinions and knowledge among the companies. Inclusion of genotyping in special populations (e.g. the elderly, paediatric, renal impairment) may help	There is no need to change the should be as in all cases, it is stated that the effect on these factors as

	assess that differences of genotype distribution with the comparator population do not confound or alter interpretation of PK results. However it is suggested that the wording in this section and section 3 be altered to better reflect (a) metabolism changes at both ends of the age spectrum (i.e. very young and very old) and (b) most importantly, recognize the emerging nature of PG influence on PK in these special populations and that it is unclear as to the impact of PK/PG data on key decision-making for clinical applications and/or for regulatory authorities. Recommend rewrite as per Theme 3 ▪ "**should be**" text needs replacement by, for example, 'may be' or 'suggest' ▪ text to be added on '*consideration of a PK/PG study or approach in special populations needs to be considered in context, relative to the drug development question being addressed and guided by the assembled evidence.*	well as the need for specific recommendations in the SPC should be considered. This reflects the current regulatory practice. The same is true to impaired and immature organ function. Regarding enzyme expression in the very old,.there is little data on effects on specific enzymes and it is less likely that the effects of age on enzyme contribution in these patients would be as marked as in the very young children. Still, we have added the following text: " Although less pronounced than in infants and toddlers, also in the very old differences in metabolism as compared to adults may occur." Considering the proposed additional text: Although we agree that PG should be seen in relationship with other factors, we do not think this has to be specifically mentioned in this section.

SECTION 8 **Treatment recommendations based on genetically determined differences in exposure**		
Section no. + paragraph no.:	**Comment and Rationale**	**Outcome**
8.	This section is important in that it impacts medical practice and thus labels/SPCs and eventually approvals--as such the text presents a **substantial departure from current practice. We would suggest that it is reworded** with the intent that any proposed difference in practice has to be 'different enough to make a difference'. A proposed working definition of 'different enough' might be a clinically meaningful difference to alter a prescribing decision by a medical practitioner. Recommend rewording as per Key Theme 3 ▪ The changes should ideally be based on further dialogue and exchanges among key stakeholders (regulators, industry, medical practitioners). A workshop or roundtable is proposed which includes experts in PG and PK as well as key stakeholders.	In one way, the text in this section is a step forward from current practice. On the other hand, it is not. These issues are currently discussed during the assessment of drugs metabolised by a polymorphic enzyme when effect of PG on the PK has clinical relevance. Usually, alternative I can be chosen and effort is made for the dose titration schedule to be suitable for the deviating genotypes. It titration is not feasible or clinically not suitable, other options, including PG based dosing are discussed and evaluated in relation to the clinical consequences of the deviating exposure. One of the main issues regarding PG based dosing has been the availability

		of PG analysis. However, PG analysis is becoming more widespread and the availability will most certainly be improved in accordance with clinical need. No change to the text is needed as there are alternatives to consider and discuss and as the need for treatment recommendations is driven by the clinical consequences of the polymorphisms.

(c) *FUTURE WORKSHOP*		
Section no. + paragraph no.:	**Comment and Rationale**	**Outcome**
	Future Workshop: This reflection paper has raised valuable awareness and identified areas which would benefit from further debate. It will be important to now work together with other key stakeholders in a proactive manner. A **future workshop** could take different formats however the main elements of the format would need to facilitate interactive dialogue, sharing of learning's, and fostering an output that could be used to finalise the reflection paper on PK/PG studies in drug development.	A future workshop on this paper will indeed be organised in due course.