Pharmacogenetic-Pharmacokinetic Interactions in Drug Marketing Authorization Applications via the European Medicines Agency Between 2014 and 2017

Marc Maliepaard[1,2,*], Timi Toiviainen[1,3], Marie L. De Bruin[3,4] and Didier Meulendijks[1]

This study aimed to determine to which extent data on potential pharmacogenetic-pharmacokinetic (PG-PK) interactions are provided to, and assessed by, the European Medicines Agency (EMA) in novel drug marketing authorization applications (MAAs), and whether regulatory assessment of PG-PK interactions is adequate or could be optimized. For this purpose, we retrospectively analyzed MAAs of small molecule drugs assessed by the EMA between January 2014 and December 2017. As per two key requirements in the EMA's guideline, we analyzed cases where (i) a single functionally polymorphic drug metabolizing enzyme (DME) metabolizes > 25% of the drug, or (ii) the drug's PK shows high interindividual variability not explained by other factors than PG. Results showed that, of 113 drugs analyzed, 53 (47%) had ≥ 1 functionally polymorphic DME accounting for > 25% of the drug's metabolism, yielding 55 gene-drug pairs. For 36 of 53 (68%) of the products, CYP3A4 was the major DME. Compliance with European Union (EU) guidance on PG-PK issues in drug development was notably different for CYP3A4 substrates vs. non-CYP3A4 substrates. Adequate PG-PK data were provided during registration in 89% (16/18) of cases concerning non-CYP3A4 substrates, compared with 32% (12/37) of cases concerning CYP3A4 substrates. Concluding, PG-PK interactions related to non-CYP3A4 substrate drugs were, in general, addressed adequately in EU MAAs. PG-PK information on CYP3A4 substrates was available less frequently, despite some available evidence on the functional relevance of *CYP3A4* polymorphisms. A more harmonized approach toward assessment of PG-PK issues in EU MAAs seems warranted, and a discussion on the relevance of *CYP3A4* polymorphisms, such as *CYP3A4*22*, is recommended.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Guidelines from the European Medicines Agency (EMA) are available for assessing pharmacogenetic-pharmacokinetic (PG-PK) interactions in marketing authorization applications of novel drugs.

WHAT QUESTIONS DID THIS STUDY ANSWER?

☑ This study investigated to what extent potential (PG-PK) interactions with novel drugs are included in drug development plans, and are assessed by regulators in accordance with current EMA guidelines on PG-PK interactions.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ This study shows that PG-related gene–drug interactions were, in general, addressed as required per the EMA's PG-PK guideline, when it concerned non-CYP3A4 substrate drugs. Adequate PG-PK data were available at approval for 16 of 18 of drugs (89%). However, when it concerned CYP3A4 substrates, PG-PK information was available at the time of registration in only a minority of cases (i.e., for 12/37 (32%) of the novel drugs). Lack of recognition of CYP3A4 as a functionally polymorphic enzyme with potential clinical relevance, and, in particular, the relevance of poor metabolizer genotypes, such as *CYP3A4*22*, is the likely cause for this finding.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ *CYP3A4* genotypes have in recent years been shown to have a clinically relevant impact on the PK of some drugs that are CYP3A4 substrates. The findings from this study warrant increased awareness towards the potential for PG-PK interactions with drugs that are CYP3A4 substrates during drug development and during assessment of MAAs for novel drugs in the EU.

[1]Dutch Medicines Evaluation Board (CBG-MEB), Utrecht, The Netherlands; [2]Department of Pharmacology and Toxicology, Radboud University Medical Centre, Nijmegen, The Netherlands; [3]Copenhagen Centre for Regulatory Science, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark; [4]Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands. *Correspondence: Marc Maliepaard (m.maliepaard@cbg-meb.nl)

Received December 27, 2019; accepted March 14, 2020. doi:10.1002/cpt.1834

There is large variability in how patients respond to medicines, and the efficacy and safety of drugs vary widely for virtually all drugs. Patient characteristics that affect drug pharmacokinetics (PK) and/or pharmacodynamics (PD) contribute to this variability, including factors such as age, weight, sex, renal function, and hepatic function. Over the past decades, it has become clear that also genetics (i.e., DNA characteristics) can have a key influence on drugs' PK/PD and consequently on efficacy and safety.[1]

Pharmacogenetics (PG) is the study of associations between patients' genetics and drug response. The association between genetic polymorphisms in drug metabolizing enzymes (DMEs) and drug PK/PD has been studied extensively, and functionally polymorphic DMEs are often referenced in drug labeling.[2,3] Cytochrome P450 enzymes are the most well-known examples of functionally polymorphic DMEs. In case of a functionally polymorphic DME, based on the degree of activity of DMEs as determined by phenotyping or predicted by genotype, patients are typically classified as: extensive metabolizer (normal metabolic activity), ultrarapid metabolizer (above-average activity), intermediate metabolizer (below-average activity), or poor metabolizer (PM; strongly reduced activity). Clinically relevant impact of DME phenotype has been demonstrated for many drugs, including tricyclic antidepressants, opioids, and cardiovascular medications.[1]

In general, an enzyme is considered polymorphic when the most common ("wild-type") allele has a frequency of ≤ 99% (i.e., at least 1% of the subjects has a polymorphic gene sequence).[4] For a number of DMEs (e.g., CYP2D6, CYP2C9, CYP2C19, and CYP3A4), polymorphic genotypes represent up to 40%, 28%, 30%, and 8%, respectively, of the total population.[5,6] Analogous to inhibition of a DME by concomitantly administered drugs, which may lead to clinically relevant increases in blood concentrations of the drug, gene–drug interactions have the potential to cause clinically relevant effects on drug safety and efficacy in clinical practice.

A key example of a relevant gene–drug interaction is the interaction between *CYP2C19* genotype and clopidogrel efficacy in patients with acute coronary syndrome.[7] Because clopidogrel is a prodrug that needs to be activated *in vivo* by CYP2C19, reduced CYP2C19 activity can lead to reduced pharmacological effect. Although individual studies on clopidogrel and CYP2C19 did not always show consistent outcomes, a large meta-analysis indicated that clopidogrel-treated patients with acute coronary syndrome undergoing percutaneous coronary intervention who are *CYP2C19*2* heterozygotes or homozygotes (combined frequency ~ 28% in white patients) have an increased risk for major adverse cardiovascular events as compared with *CYP2C19*1* homozygotes and increased risks of stent thrombosis.[8] The growing body of literature implicating *CYP2C19*2* (and probably other loss-of-function alleles) in adverse clopidogrel responses has prompted the US Food and Drug Administration (FDA) to implement a "black box warning" on the increased risk for major adverse cardiovascular events, and, in the European Union (EU) clopidogrel Summary of Product Characteristics (SmPC), a warning is included regarding lower formation of active metabolites of clopidogrel and a smaller effect on platelet function in patients who are poor CYP2C19 metabolizers.[9,10] Examples of other drugs for which PG-PK interactions are considered important are eliglustat, approved by the FDA and the European Medicines Agency (EMA) in 2014/2015 for the treatment of Gaucher disease type 1 specifically in patients who are poor, intermediate, or extensive CYP2D6 metabolizers,[11,12] and siponimod, a multiple sclerosis drug being metabolized by CYP2C9, for which the FDA and the EMA approved recommended dosage is determined by *CYP2C9* genotype.[13,14] These examples show that availability of PG-PK data and assessment of these data by regulators can be critical to avoid safety and efficacy issues and can serve as a tool to tailor drug treatment to the right patients at the right dose.

Besides relatively common polymorphisms, the cumulative frequency of rare variants, which lead to PM phenotypes may also be relevant, such as for CYP3A4 and to a lesser extend CYP2C9, and these rare variants may ultimately contribute substantially to metabolic variability in the patient population.[15] However, because at this stage no regulatory requirements are posed on such rare variants, this will not be included in this paper.

Of note, although metabolic activity of the most prominently involved CYP DME, CYP3A4, is known to be highly variable between subjects, the *CYP3A4* gene was until recently considered not to have functionally relevant polymorphisms.[16,17] However, in 2011 Wang *et al*. identified the *CYP3A4*22* allele, a polymorphism that has since been associated with PG-PK interactions (e.g., lower clearance of tacrolimus; 30% lower dose requirements) and cyclosporin A (53% higher concentration) in renal transplant patients, and 2.5-fold higher serum concentrations of quetiapine.[6,18] *CYP3A4*22* has also been reported to substantially influence the PK of statins[1,6,19] and different drugs used in oncology, including sunitinib, pazopanib, and docetaxel.[20–22] For other drugs, there are contradictory reports on the effect of *CYP3A4*22* on PK (e.g., for voriconazole,[23,24] and clopidogrel).[25] Overall, however, the available evidence seems sufficient to indicate that *CYP3A4* polymorphisms, and specifically *CYP3A4*22*, should be considered during development of novel drugs, which are substrate for CYP3A4.

In view of the importance of having data regarding PGs and potential PG-PK interactions available prior to marketing authorization/drug approval, the EMA released in 2012 the "*Guideline on the use of pharmacogenetic methodologies in the pharmacokinetic evaluation of medicinal products*" (hereafter: the EMA PG-PK guideline).[26] This guideline provides a framework for using PG data during drug development. The FDA and the Pharmaceuticals and Medical Devices Agency (PMDA) in the United States and Japan, respectively, have published similar guidance.[27]

The EMA PG-PK guideline describes two key criteria to provide guidance on when PG-PK should be studied in confirmatory studies: (i) if there is a single PK enzyme that metabolizes > 25% of the drug *in vivo* based on early clinical studies and is known to be polymorphic, and (ii) when the drug's PK shows large interindividual variability that cannot be explained by other intrinsic or extrinsic factors.

In the EMA PG-PK guideline, a cutoff of 25% is defined, above which the clinical relevance of a genetic polymorphism should be investigated during the drug development phase.[26] This 25%

cutoff is in line with the cutoff that is applied by the EMA in case of drug–drug interactions (see EMA *Guideline on the investigation of drug interactions*).[28] This cutoff seems reasonable, because, for a PM, the effect of the genetic polymorphism on exposure of a drug may be comparable with the effect of a strong inhibitor of the enzyme involved. The term "high interindividual variability" is not further specified in the EMA guideline, although, in the EMA *Guideline on Investigation of Bioequivalence*, a cutoff for high PK variability of 30% is described.[29]

To which extent availability of PG data in the initially submitted dossier for the marketing authorization application (MAA) and regulatory assessment of the MAA is in line with current guidelines has not been systematically studied previously. In this study, we analyzed all MAAs that were submitted to the EMA via the Centralized Procedure between January 2014 and December 2017, in order to determine how PG was implemented in the drug development plan, how these PG data subsequently was assessed, and whether the assessment of PG-PK issues is currently adequate or could be optimized.

METHODS

Study design and objectives

We performed a retrospective analysis of novel drugs that were assessed by the EMA between January 2014 and December 2017. In part 1 and 2 of the analysis, we investigated to which extent the above-mentioned requirements of the EMA guideline (1 and 2, respectively) were followed. In both parts of the study, the objective was to determine the extent of availability of PG-PK data in the initially submitted dossier for the MAA as well as how the data were assessed by the EMA. The results of these analyses were used to determine whether assessment of PG-PK issues in EU MAAs is currently adequate or could be optimized. The availability of PG-PK data in MAAs over time within the 2014–2017 study period was also assessed.

Data collection

All medicinal products for human use, which were assessed via the Centralized Procedure by the EMA and were either granted or refused marketing authorization between January 2014 and December 2017 (n = 320; **Figure 1**), were identified and retrieved via the EMA database (https://www.ema.europa.eu). Only products with a full dossier, for a novel medicinal product were included. Applications building on previously authorized medicines (e.g., generics (n = 41) and biosimilars (n = 24)), were excluded, because, for these products in general, no new PG-PK data are submitted. Finally, biologicals (n = 78) were excluded from the analysis, becaused such pharmaceuticals are metabolized by pathways for which the effect of PGs is not well-established (e.g., proteolytic pathways). This selection yielded 113 small molecule products, which were included in the analysis.

Data on the drug's metabolic pathways, the DMEs involved, and the drug's general PK, including interindividual variability in PK, were extracted from publicly available data sources (i.e., the EMA European Public Assessment Report (EPAR), the SmPC, the EMA website, as well as from internal data sources at the Dutch Medicines Evaluation Board (MEB) including assessment reports of the EU Rapporteur and Co-Rapporteurs). In addition, for each drug, the scientific literature was searched using PubMed and prespecified search strings to collect information on PG-PK interactions (details provided in **Table S1**).

If a single enzyme's contribution to the drug's metabolism was > 25% *in vivo* (i.e., in human subjects or patients), the respective DME was considered to be a "major DME" for the purpose of this study (i.e., an enzyme with a major contribution to the drug's PK).

Information on the relevance of genetic polymorphisms

The importance of genetic polymorphisms for the identified major DMEs was determined based on the available scientific literature. If the polymorphism was known to cause interindividual differences in exposure of drugs metabolized by the respective DME and it was determined that this could potentially influence the drug's efficacy and/or safety (as determined by consensus between three of the investigators: M.M., T.T., and D.M.), and, in addition, the frequency of the functional polymorphism was known to be > 1% in white populations,[26] the enzyme was determined to be a "known functionally polymorphic DME."

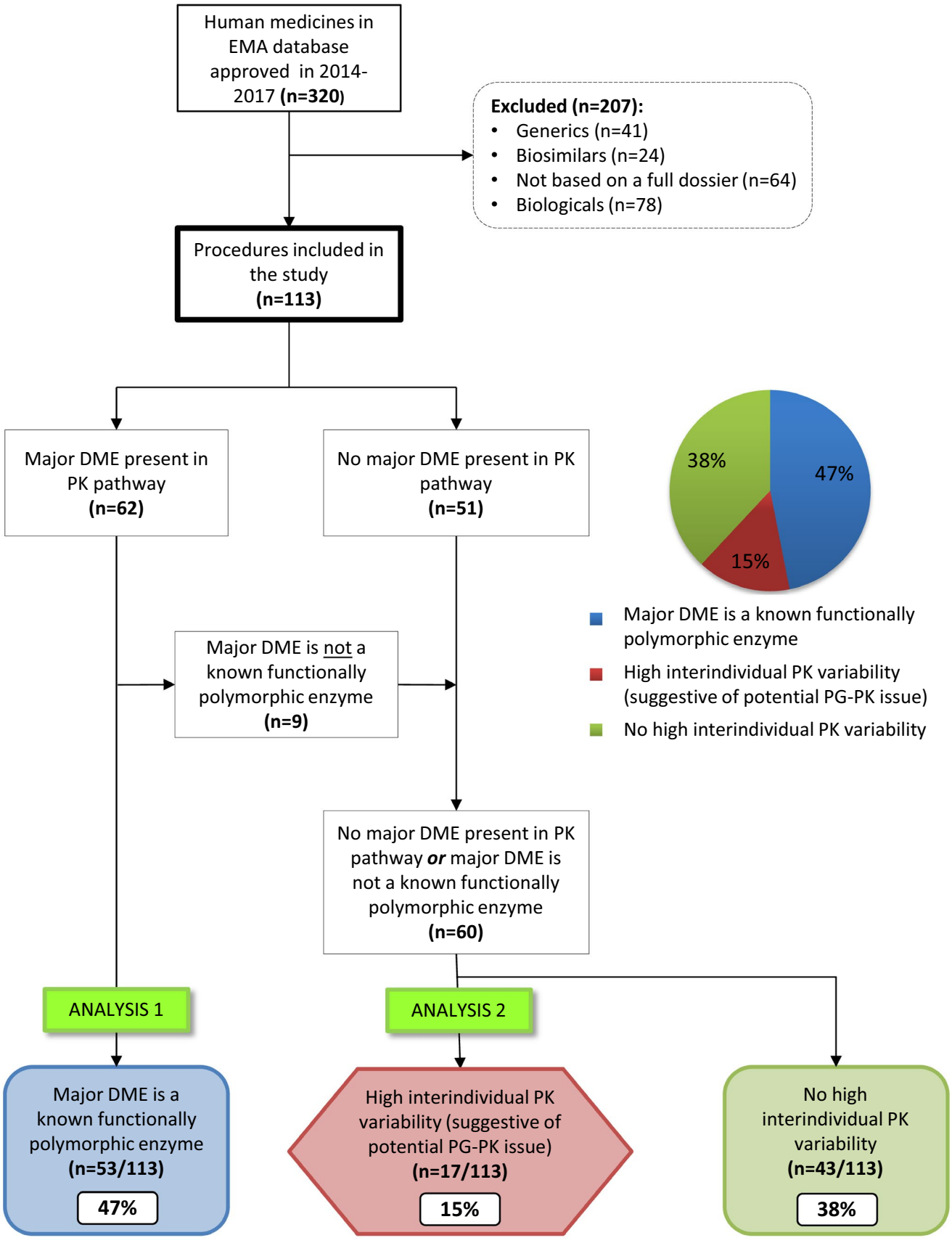
Products for which the major DME was known to be functionally polymorphic (hereafter "major functionally polymorphic DME") were included in the primary analysis (Analysis 1). The remaining products for which no major functionally polymorphic DME was identified were included in the secondary analysis (Analysis 2) only in case the drug's PK showed high interindividual variability (> 30% as indicated in the introduction) that could not be explained by other intrinsic or extrinsic factors, like age, weight, sex, and renal or hepatic function. This is generally tested via a population PK model combining PK data from all clinical studies in the MAA dossier.

Data analysis

Analysis 1, involving drugs with a known major functionally polymorphic DME, was conducted in sequential steps. First, it was determined whether or not a major functionally polymorphic DME was acknowledged by the applicant and/or the assessors/EMA Committee for Medicinal Products for Human Use (CHMP), subsequently whether or not PG-PK data were provided by the applicant, whether and at which stage additional PG-PK data were requested by the CHMP, and whether and how PG-PK data were provided as a result of the CHMP's questions. The data were summarized and analyzed using descriptive statistics.

Analysis 2, involving drugs without a known major functionally polymorphic DME but with identified highly variable PK, followed a similar approach but focused on how frequently the CHMP raised questions about the potential impact/relevance of interindividual variability in PK not explained by other factors as mentioned above, how often these questions were asked specifically in relation to PG-PK, and whether or not the applicant provided PG-PK data as a result of the questions raised.

Figure 1 Flowchart describing selection of marketing authorization applications for inclusion in Analysis 1 and Analysis 2. Products with a known functionally polymorphic major DME were included in Analysis 1 and products with an indication for involvement of a functionally polymorphic DME based on high interindividual PK variability were included in Analysis 2. Products with no indication for functionally polymorphic DMEs based on PK variability and that did not have a known major functionally polymorphic DME involved in their metabolism, were excluded from further analyses. The pie chart represents the proportion of products having (blue) or not having (green) a known functionally polymorphic DME, or display high PK variability (red). The major functionally polymorphic DMEs included CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CES1, SULT1A1, UGT1A1, and UGT1A9. The nine major DMEs that were considered not to have relevant functionally polymorphisms were cathepsin A, UGT1A6, aromatic L-amino acid decarboxylase, aldehyde oxidase, and microsomal epoxide hydrolase. DME, drug metabolizing enzyme; EC, European Commission; EMA, European Medicines agency; PK, pharmacokinetics: high interindividual variability means > 30%.


Human medicines in EMA database approved in 2014-2017 (n=320)
Excluded (n=207):
• Generics (n=41)
• Biosimilars (n=24)
• Not based on a full dossier (n=64)
• Biologicals (n=78)
Procedures included in the study (n=113)
Major DME present in PK pathway (n=62)
No major DME present in PK pathway (n=51)
Major DME is not a known functionally polymorphic enzyme (n=9)
No major DME present in PK pathway or major DME is not a known functionally polymorphic enzyme (n=60)
ANALYSIS 1
ANALYSIS 2
Major DME is a known functionally polymorphic enzyme (n=53/113)
47%
High interindividual PK variability (suggestive of potential PG-PK issue) (n=17/113)
15%
No high interindividual PK variability (n=43/113)
38%
38%
47%
15%
Major DME is a known functionally polymorphic enzyme
High interindividual PK variability (suggestive of potential PG-PK issue)
No high interindividual PK variability

Last, to determine how the PG-PK data were ultimately reflected in the product SmPC, the SmPCs of the products included in both analyses were analyzed and the SmPCs PG-PK data summarized.

RESULTS

For 62 of 113 (55%) of the included products, a major DME was involved in the drug's metabolism (**Figure 1**). Of these 62 products, there were 9 products with major DMEs, which were considered not to have known genetic polymorphisms of clinical relevance based on current scientific knowledge (i.e., cathepsin A and UGT1A6, aromatic L-amino acid decarboxylase, aldehyde oxidase, and microsomal epoxide hydrolase). After exclusion of these 9 products, 53 products (47% of 113) remained, which were identified as having a major functionally polymorphic DME. Two products had two potential gene–drug interactions, yielding 55 gene-drug pairs. These products were included in Analysis 1. The functionally polymorphic DMEs involved were CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CES1, SULT1A1, UGT1A1, and UGT1A9.

From the 60 of 113 products for which no major functionally polymorphic DME was identified, 17 products (15% of 113) were identified as having high interindividual PK variability (i.e., a potential indication for PG-PK effects), and were included in Analysis 2. A total of 43 products (38% of 113) did not have high PK variability and did not have a major functionally polymorphic DME involved in their metabolism, and these products were, therefore, excluded from further analysis (**Figure 1**).

Table 1 presents an overview of products and characteristics for all the products included in Analysis 1 and Analysis 2.

Analysis of drugs metabolized by a known major functionally polymorphic DME (Analysis 1)

For 37 of 53 (70%) of the products that were included in Analysis 1, CYP3A4, CYP3A5, or CYP3A4/5 (32, 1, and 4 products, respectively) was identified as the major functionally polymorphic DME (**Figure 2**). Because of the highly similar substrate selectivity between these DME isoforms, these enzymes are often referred to as one group, CYP3A4/5.[30] The next most prominent DMEs were UGT1A1, CYP2D6, and CES1 (3 products (6%) each). The remainder of the DMEs occurred for only one or two products each. Two of the products had two major functionally polymorphic DMEs (i.e., CYP2C8 and CES1; and CYP2D6 with CYP3A4) and, therefore, among 53 drugs, 55 gene-drug pairs were identified.

Of the 53 drugs in Analysis 1, the applicant provided PG-PK data considering the relevant functionally polymorphic DME in the initially submitted dossier for the MAA in 9 of 53 (17%) of applications (**Figure 3**). In the remaining 44 of 53 procedures (83%), PG-PK data were not provided by the applicant in the initially submitted dossier. Within these procedures, in 9 of 44 (20%) of these cases in which there was a major functionally polymorphic DME involved in the drug's PK (in light of currently available scientific knowledge and in the context of this study), this was not recognized nor questioned by the EMA during assessment of the application. In all nine of these cases, the polymorphic DME involved was CYP3A4. The presence of a major functionally polymorphic DME was acknowledged and/or questioned by the regulatory authorities during assessment of the application in the remaining 35 of 44 (80%) procedures. However, in only 18 of these 35 cases (51%), additional PG-PK data were requested. In 8 of these 18 cases, the question concerned the potential relevance of CYP3A4 polymorphisms.

As shown in **Figure 3**, in 4 of 35 of the cases (11%) in which a major functionally polymorphic DME was identified by the CHMP, no PG-PK data were requested, and no statement on the expected relevance of the polymorphism was provided by the EMA. Further, in 13 of 35 cases (37%), it was *a priori* concluded by CHMP that such polymorphisms were not expected to be clinically relevant. The latter two situations combined, in which no further data were requested, add up to 17 of 35 (49%) of the cases in which a major functionally polymorphic DME was identified by the CHMP. In 16 of these 17 cases, the potentially relevant DME involved was CYP3A4, another one concerned CYP2C8.

In all of the 18 cases where questions were raised by the CHMP, PG-PK data were subsequently submitted by the applicant, either in the form of published data or in-house data, and, in all these cases, the questions were considered answered adequately by the applicants according to the Rapporteurs/CHMP. In 4 of 18 cases (22%), the applicant provided a PG-PK study on the major DME as a postauthorization measure and in 13 cases (n = 13/18; 72%) the applicant referred to the scientific literature or the dossier in their answers without conducting further studies or analyses. There was one case (1/18; 6%) where the applicant provided a new PG study before the marketing authorization as a result of the question raised during assessment of the dossier.

Overall, PG-PK data had been provided at the end of the assessment procedure in 27 (9 + 18; green boxes in **Figure 3**) of 53 procedures (51%), and were not submitted/available in the remaining 26 procedures (49%; 9 + 4 + 13; red boxes in **Figure 3**).

Figure 4 illustrates the relationship between the type of enzyme involved in procedures in which a major functionally polymorphic DME was identified (included in Analysis 1) and whether or not data to address the issue of potential PG-PK issues were provided during the procedure. This figure illustrates that for all DMEs combined excluding CYP3A4/5, PG-PK data were provided during the assessment of the procedure in 16 of 18 cases (89%). In cases where CYP3A4/5 was involved, on the other hand, in only 12 of 37 cases (32%) PG-PK data were provided.

Since the regulatory guideline on PG-PK was issued in 2012, the proportion of applications where PG-PK data were requested was analyzed by year of drug approval. No clear pattern over the years analyzed was noted, with PG-PK data concerning major functionally polymorphic DMEs provided in 53% of the procedures in 2014 (n = 9/17), 56% in 2015 (n = 9/16), 60% in 2016 (n = 6/10), and 30% in 2017 (n = 3/10).

Analysis of drugs with high interindividual variability in PK (Analysis 2)

In line with the PG-PK guideline, for drugs that showed high interindividual variability in area under the curve (AUC) which could not be explained by known factors other than PG, questions

Table 1 Overview and characteristics of small molecule products included in Analysis 1 and Analysis 2

	Major DME is a known functionally polymorphic enzyme		Large interindividual PK variability	
Product characteristics	***n* = 53**	**(%)**	***n* = 17**	**(%)**
Authorization status				
Authorized	47	88.7	17	100
Authorized and later withdrawn	1	1.9	0	0
Refused	5	9.4	0	0
Year of commission decision				
Granted marketing authorization				
2017	8	15.1	4	23.5
2016	10	18.9	2	11.8
2015	16	30.2	4	23.5
2014	14	26.4	7	41.2
Refused marketing authorization				
2017	2	3.8	0	0.0
2016	0	0.0	0	0.0
2015	0	0.0	0	0.0
2014	3	5.7	0	0.0
Procedure started				
2017	1	1.9	1	5.9
2016	8	15.1	2	11.8
2015	8	15.1	3	17.6
2014	15	28.3	3	17.6
2013	15	28.3	6	35.3
2012	6	11.3	2	11.8
Type of authorization				
Conditional approval[a]	3	5.7	1	5.9
Exceptional circumstances	0	0.0	0	0.0
Normal	50	94.3	16	94.1
Orphan status				
Yes	16	30.2	3	17.6
No	37	69.8	14	82.4
New active substance[b]				
Yes	48	90.6	15	88.2
No	5	9.4	2	11.8
ATC coding[c]				
A-Alimentary tract and metabolism	5	9.4	3	17.6
B-Blood and blood forming organs	2	3.8	0	0.0
C-Cardiovascular system	4	7.5	1	5.9
D-Dermatologicals	0	0.0	0	0.0
G-Genito-urinary system and sex hormones	1	1.9	0	0.0
H-Systemic hormonal preparations, excluding sex hormones and insulins	0	0.0	0	0.0
J-Anti-infectives for systemic use	8	15.1	6	35.3
L-Antineoplastic and immunomodulating agents	19	35.8	4	23.5
M-Musculoskeletal system	1	1.9	0	0.0
N-Nervous system	8	15.1	2	11.8

(Continued)

Table 1 (Continued)

Product characteristics	Major DME is a known functionally polymorphic enzyme		Large interindividual PK variability	
	n = 53	(%)	*n* = 17	(%)
P-Antiparasitic products, insecticides, and repellents	0	0.0	0	0.0
R-Respiratory system	2	3.8	0	0.0
S-Sensory organs	0	0.0	0	0.0
V-Various	1	1.9	0	0.0
No coding	2	3.8	1	5.9
Route of administration				
Oral	49	92.5	15	88.2
Inhalation	2	3.8	1	5.9
s.c./i.v.	2	3.8	1	5.9

ATC, Anatomical Therapeutic Chemical Classification System; DME, drug metabolizing enzyme; PK, pharmacokinetic.
[a]Conditional approval current status was based on data provided at the European Medicines Agency (EMA) website in February 2018. [b]New active substance status as concluded by the EMA during registration procedure. [c]ATC coding was based on the ATC/DDD Index 2018 (https://www.whocc.no/atc_ddd_index/).

about interindividual variability were asked in 16 of 17 procedures (94%). In eight procedures (50%), these questions focused on interindividual variability without specifying potential causes. In one procedure (6%), the question was specifically related to PG-PK, and in seven additional cases (44%), there were separate questions about both PG-PK and interindividual PK variability. In 8 of 16 cases (50%), the applicant provided a discussion on (published or in-house) PG-PK data as a result of the question. None of the products included in Analysis 2 were ultimately considered by the CHMP to possess clinically relevant PG-PK interactions, as evident from the currently included information in the SmPC for the products involved.

PG-PK information in product labeling/SmPC

Of the 53 products that had a major functionally polymorphic DME involved in the drug's metabolism and of which 47 are currently on the market, 12 products (26%) have information regarding PGs of the respective DME in the SmPC. For nine of these products that are mentioned in the SmPC, the potential importance of PG-PK was recognized by the applicant in the initially submitted dossier for the MAA, for three products information on PG-PK was requested by CHMP during the assessment procedure. **Table 2** illustrates in which sections the information on PK-related PGs was included. For six products, the SmPC contains statements describing that the PG-PK interactions are considered

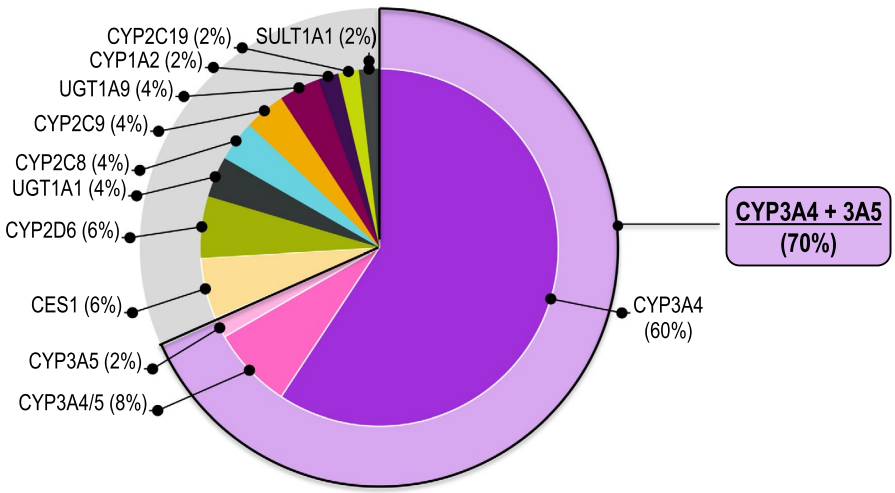


Figure 2 Frequency of the major functionally polymorphic DMEs included in the Analysis 1. The inner circle represents the frequency of individual DMEs, the outer purple circle represents the total frequency of CYP3A4 and CYP3A5. The total number of DMEs exceed the number of products (53 = 100%; *n* = 55), because two of the products had two major gene–drug interactions, so two major functionally polymorphic DMEs involved in their metabolism. DME, drug metabolizing enzyme.

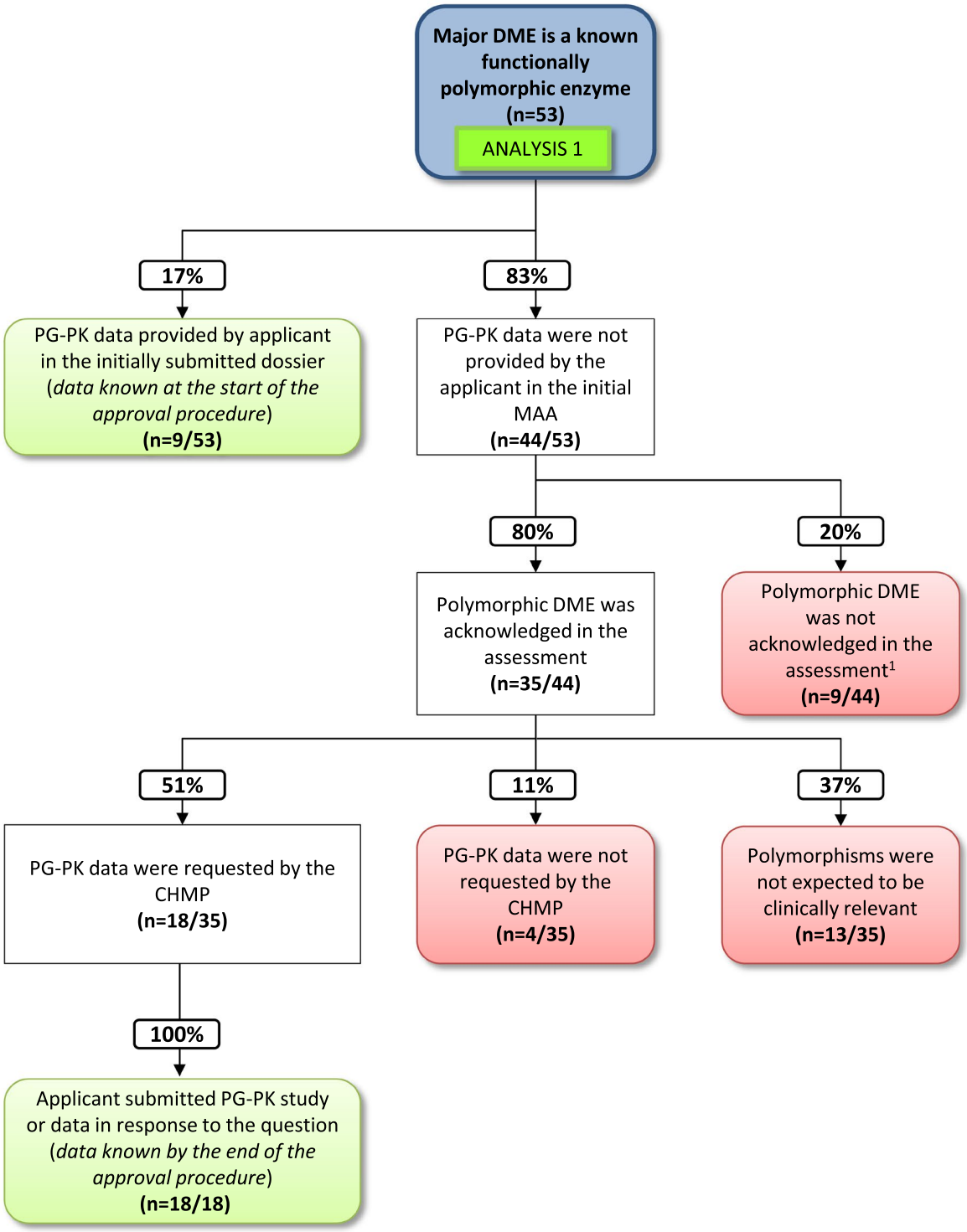


Figure 3 Flowchart describing interaction between the applicant and the regulatory authorities in case a major functionally polymorphic DME was present (Analysis 1). In total, PG-PK data were provided in 9 + 18 = 27 of 53 procedures (51%; indicated in green boxes) and were not submitted in 9 + 4 + 13 = 26 of 53 procedures (49%; indicated in red boxes). The clinical relevance of the gene–drug interactions was decided upon by EMA Committee for Medicinal Products for Human Use during assessment of the MAA, generally based on the magnitude of (expected) effect on exposure by functionally polymorphic DME genotypes in the context of the therapeutic window of the drug. N.B. % values in the fourth row do not add up to 100% due to rounding issues. DME, drug metabolizing enzyme; PG-PK, pharmacogenetic-pharmacokinetic.

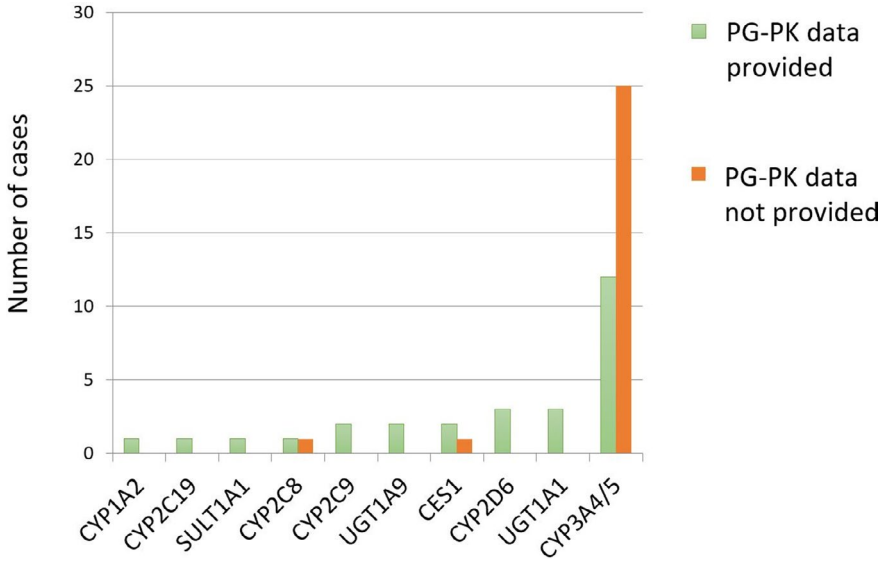


Figure 4 Relationship between type of functionally polymorphic DME and whether or not data regarding the potential PG-PK interaction were provided during the assessment procedure. Applications in which PG-PK data on an identified functionally polymorphic DME were provided are indicated in green, vs. cases in which no data were provided shown in orange. The total number is 55 (gene-drug pairs), in the context of 53 procedures/drugs. DME, drug metabolizing enzyme; PG-PK, pharmacogenetic-pharmacokinetic.

clinically relevant, including those resulting in different dosing recommendations or increased risk of adverse drug reactions for genetic subpopulations. Of these six products, four were already recognized in the initially submitted dossier for the MAA, and two were recognized by the CHMP during assessment. The clinical relevance of the gene–drug interactions, as described in the SmPC, was decided upon by the CHMP during assessment of the MAA, generally based on the magnitude of (expected) effect on exposure by functionally polymorphic DME genotypes in the context of the therapeutic window of the drug. In case functional polymorphisms of the DME were not considered to be clinically relevant, only descriptive data were provided in section 5.2 of the SmPC. **Table 3** shows that PG-PK data were included in the SmPC only if the PG-PK data were provided/discussed during the procedure.

DISCUSSION

The purpose of this study was to evaluate how PK-related gene–drug interactions were implemented in the drug development plan, how this was assessed for novel drugs authorized in the European Union by the EMA, and whether or not regulatory assessment of potential PG-PK interactions is currently adequate or could be optimized.

We found that for medicinal products registered in the European Union between 2014 and 2017, in only 51% (27/53) of the procedures where a functionally polymorphic DME played a major role in the drug's metabolism, PG-PK information was ultimately included in the registration dossier at the time of registration. Further, although in 80% (35/44) of the procedures where no PG-PK data were provided upfront by the applicant, a potential PG-PK issue for the novel drug was acknowledged during assessment by CHMP, additional PG-PK data were only requested by CHMP in 51% (18/35) of these cases. Last, in ~ 20% (9/44) of the procedures involving a functionally polymorphic DME with potential clinical relevance according to our analysis, but where no PG-PK data were provided by the applicant, the potential PG-PK issue was not acknowledged at all by the applicant nor regulators. We noted no trend toward increase in the availability of PG-PK data for novel drugs over time, acknowledging, however, the relatively short time period analyzed. Further, although the PG-PK guideline states that a gene–drug interaction may be mimicked by a drug-interaction study in order to predict consequences of specific genetic polymorphism in patients, we did not encounter such data in the dossiers that were included in this study.

These findings may suggest that either the PG-PK guideline, issued in 2012, is not always followed by applicants and regulators, or, perhaps more likely, that there are varying interpretations on which are relevant functionally polymorphic DMEs. In this respect, it is important to note the role that CYP3A4 had on the outcome of our analysis. As indicated in the introduction, the currently available evidence suggests that a potentially relevant effect of *CYP3A4* genotypes, in particular *CYP3A4*22*, on the PK of drugs, which are CYP3A4 substrate cannot be excluded *a priori*, which is why we considered *CYP3A4* as a functionally polymorphic DME in this analysis. Lower compliance with the PG-PK guideline was mainly seen in regard to CYP3A4 substrates, most likely as a result of the fact that *CYP3A4*22* was not consistently acknowledged by industry and assessors of regulatory authorities as potentially clinically relevant. Therefore, a separate discussion for products where CYP3A4 is the major DME and products for which it is not is warranted.

In our study, we observed that for 25 (i.e., all except one) of the 26 of 35 procedures where the polymorphic DME was not acknowledged in the assessment, no PG-PK data were requested by regulators, or polymorphisms were not expected to

Table 2 Summary of PG-PK information provided in the product information of 12 products that had information on PG in the SmPC

	SmPC section where PG-PK data is included								
Polymorphic DME discussed in SmPC	4.1 Therapeutic indications	4.2 Posology and method of administration	4.3 Contraindications	4.4 Special warnings and precautions for use	4.5 Interaction with other medicinal products	4.8 Undesirable effects	5.1 Pharmacodynamic properties	5.2 Pharmacokinetic properties	SmPC indicates gene-drug interaction is clinically relevant
(*n* = 12)									
CYP2C19								1	No
CYP2C9				1				1	Yes
CYP2C9					1			1	Yes
CYP2D6	1	1	1	1	1		1	1	Yes
CYP2D6		1						1	Yes
CYP2D6								1	No
CYP3A4				1				1	Yes
UGT1A1		1				1	1	1	Yes
UGT1A1								1	No
UGT1A1								1	No
UGT1A9								1	No
UGT1A9								1	No
Total	1	3	1	3	2	1	2	12	

DME, drug metabolizing enzyme; PG-PK, pharmacogenetic-pharmacokinetic; SmPC, Summary of Product Characteristics.

Table 3 Distribution of PG-PK data in the SmPC in case PG-PK was studied or not

	PG-PK data concerning major DMEs were provided (*n* = 27)	PG-PK data concerning major DMEs were not provided (*n* = 26)	Total (*n* = 53)
No PG-PK data in SmPC	15 (55%)	26 (100%)	41 (78%)
PG-PK data in SmPC – not clinically relevant	6 (22%)	0 (0%)	6 (11%)
PG-PK data in SmPC – clinically relevant	6 (22%)	0 (0%)	6 (11%)

DME, drug metabolizing enzyme; PG-PK, pharmacogenetic-pharmacokinetic; SmPC, Summary of Product Characteristics.
The clinical relevance of the gene–drug interactions was decided upon by EMA Committee for Medicinal Products for Human Use during assessment of the marketing authorization application, generally based on the magnitude of (expected) effect on exposure by functionally polymorphic DME genotypes in the context of the therapeutic window of the drug.

have clinically relevant effects (red boxes in **Figure 3**), this concerned CYP3A4/5. As shown in **Figure 4**, this led to the situation that only in 12 of 37 cases (32%) in which CYP3A4/5 was involved, PG-PK data were ultimately provided. Conversely, for non-CYP3A4/5 substrate drugs, PG-PK data were provided in the vast majority of cases (16/18; 89%). These findings suggest that the EMA PG-PK guideline is well appreciated by applicants and assessors, but that the relatively large number of products for which no PG-PK data were submitted during the assessment was mostly due to different interpretations or awareness regarding the relevance of the *CYP3A4* polymorphisms, such as *CYP3A4*22*.

Besides varying interpretations toward the relevance of *CYP3A4* polymorphisms, the fact that the drug development processes generally takes 10 years or longer[31,32] may have contributed to the finding that data on more recently identified clinically relevant polymorphisms, such as *CYP3A4*22*, were not generated at the time of the early-phase clinical studies and, hence, were not available at the time of MAA.

The results from this analysis illustrate the role that applicants and regulatory agencies jointly have in the safe and effective use of medicinal products. In a majority of the cases where a major functionally polymorphic DME was involved but the initially submitted dossier for the MAA did not contain data on potential PG-PK interactions, only after questions from the regulatory authorities' data were provided/discussed. Further, it was noted that for two of the drugs in our dataset for which PG-PK data were only provided upon request by the CHMP, the outcome was ultimately considered clinically relevant, and information was included in the SmPC.

The fact that CYP3A4 was not consistently acknowledged as a potentially important functionally polymorphic DME during MAA assessment suggests there is room for improved harmonization in the European Union regarding which functionally polymorphic DMEs should be considered as "known functionally polymorphic enzymes," with potential clinically relevant impact. We recommend that a list of acknowledged functionally polymorphic DMEs with potential clinical relevance be published by the regulatory agencies (e.g., as an appendix to the PG-PK guideline, which was developed by the EMA's Pharmacogenomics Working Party).[26] By doing so, both applicants and regulatory assessors can agree on which are the functionally polymorphic DMEs that should be considered as potentially clinically relevant during drug development and assessment of MAAs, and for which genes potential PG-PK interactions should be investigated during drug development.

CONCLUSIONS

This study shows that PK-related gene–drug interactions are addressed adequately in EU Centralized Procedures, as required per the EMA's PG-PK guideline, when it concerns non-CYP3A4 substrate drugs. However, where CYP3A4 substrates are concerned, assessment of PG-PK data was found to be noncompliant with current guidance in a majority of cases. This is likely the result of lack of recognition of *CYP3A4* as a functionally polymorphic enzyme, and the fact that *CYP3A4* genotypes, such as *CYP3A4*22*, do have the potential to lead to clinically relevant gene–drug interactions.

A more harmonized approach toward assessment of PG-PK issues in the context of MAAs in the European Union is warranted in order to further improve the benefit/risk balance of drugs in genetic subpopulations, and a discussion on the relevance of *CYP3A4* polymorphisms is recommended.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

FUNDING

No funding was received for this research.

CONFLICT OF INTEREST

D.M. is currently working at AstraZeneca, the research was conducted and finalized prior to start at this position. All authors declared no competing interests as defined by the American Society for Clinical Pharmacology and Therapeutics, or other interests that might be perceived to influence the results and/or discussion reported in this paper.

AUTHOR CONTRIBUTIONS

M.M., T.T., M.B., and T.T. wrote the manuscript. M.M., T.T., M.B., and D.M. designed the research. T.T. performed the research. T.T. analyzed the data.

1. Sim, S.C., Kacevska, M. & Ingelman-Sundberg, M. Pharmacogenomics of drug-metabolizing enzymes: a recent update on clinical implications and endogenous effects. *Pharmacogenomics J.* **13**, 1–11 (2013).
2. Frueh, F.W. *et al.* Pharmacogenomic biomarker information in drug labels approved by the United States Food and Drug Administration: prevalence of related drug use. *Pharmacotherapy* **28**, 992–998 (2008).
3. Ehmann, F. *et al.* Pharmacogenomic information in drug labels: European Medicines Agency perspective. *Pharmacogenomics J.* **15**, 201–210 (2015).
4. National Human Genome Research Institute (NHGRI). Genetic Testing Report-Glossary <https://www.genome.gov/10002399/genetic-testing-reportglossary/>. Accessed February 19, 2020.
5. Sim, S.C. & Ingelman-Sundberg, M. Pharmacogenomic biomarkers: new tools in current and future drug therapy. *Trends Pharmacol. Sci.* **32**, 72–81 (2011).
6. Werk, A.N. & Cascorbi, I. Functional gene variants of CYP3A4. *Clin. Pharmacol. Ther.* **96**, 340–348 (2014).
7. Scott, S.A. *et al.* Clinical pharmacogenetics implementation consortium guidelines for CYP2C19 genotype and clopidogrel therapy: 2013 update. *Clin. Pharmacol. Ther.* **94**, 317–323 (2013).
8. Mega, J.L. *et al.* Reduced-function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: a meta-analysis. *J. Am. Med. Assoc.* **304**, 1821–1830 (2010).
9. US Food & Drug Administration Drug Safety Communication: Reduced effectiveness of Plavix (clopidogrel) in patients who are poor metabolizers of the drug <https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/fda-drug-safety-communication-reduced-effectiveness-plavix-clopidogrel-patients-who-are-poor> (2010). Accessed February 19, 2020.
10. European Medicines Agency (EMA). Summary of product characteristics of Plavix (clopidogrel) <https://www.ema.europa.eu/en/documents/product-information/plavix-epar-product-information_en.pdf>. Accessed February 19, 2020.
11. US Food & Drug Administration Table of Pharmacogenomic Biomarkers in Drug Labeling <https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling>. Accessed February 19, 2020.
12. European Medicines Agency (EMA) European Public Assessment Report on Cerdelga <https://www.ema.europa.eu/en/medicines/human/EPAR/cerdelga> (2015). Accessed February 19, 2020.
13. US Food & Drug Administration News Release: FDA approves new oral drug to treat multiple sclerosis <https://www.fda.gov/news-events/press-announcements/fda-approves-new-oral-drug-treat-multiple-sclerosis>. Accessed February 19, 2020.
14. European Medicines Agency (EMA) European Public Assessment Report on Mayzent <https://www.ema.europa.eu/en/documents/smop-initial/chmp-summary-positive-opinion-mayzent_en.pdf> (2019). Accessed February 19, 2020.
15. Ingelman-Sundberg, M., Mkrtchian, S., Zhou, Y. & Lauschke, V.M. Integrating rare genetic variants into pharmacogenetic drug response predictions. *Hum. Genomics* **12**, 26 (2018).
16. Ahmed, S., Zhou, Z., Zhou, J. & Chen, S.Q. Pharmacogenomics of drug metabolizing enzymes and transporters: relevance to precision medicine. *Genomics Proteomics Bioinform.* **14**, 298–313 (2016).
17. Pinto, N. & Dolan, M.E. Clinically relevant genetic variations in drug metabolizing enzymes. *Curr. Drug Metab.* **12**, 487–497 (2011).
18. Elens, L., van Gelder, T., Hesselink, D.A., Haufroid, V. & van Schaik, R. CYP3A4 variant allele for personalizing pharmacotherapy review. *Pharmacogenomics* **14**, 47–62 (2013).
19. Klein, K. & Zanger, U.M. Pharmacogenomics of cytochrome P450 3A4: recent progress toward the 'missing heritability' problem. *Front. Genet.* **4**, 1–15 (2013).
20. Patel, N.D., Chakrabory, K., Messmer, G., Krishnan, K. & Bossaer, J.B. Severe sunitinib-induced myelosuppression in a patient with a CYP 3A4 polymorphism. *J. Oncol. Pharm. Pract.* **24**, 623–626 (2018).
21. Bins, S. *et al.* Impact of CYP3A4*22 on Pazopanib pharmacokinetics in cancer patients. *Clin. Pharmacokinet.* **58**, 651–658 (2019).
22. Sim, S., Bergh, J., Hellström, M., Hatschek, T. & Xie, H. Pharmacogenetic impact of docetaxel on neoadjuvant treatment of breast cancer patients. *Pharmacogenomics* **19**, 1259–1268 (2018).
23. Duflot, T., Schrapp, A., Bellien, J. & Lamoureux, F. Impact of CYP3A4 genotype on voriconazole exposure. *Clin. Pharmacol. Ther.* **103**, 185–186 (2018).
24. Walsh, T.J., Moriyama, B., Penzak, S.R., Klein, T.E. & Caudle, K.E. Response to 'Impact of CYP3A4 genotype on voriconazole exposure: new insights into the contribution of CYP3A4*22 to metabolism of voriconazole'. *Clin. Pharmacol. Ther.* **103**, 187 (2018).
25. Kreutz, R.P. *et al.* Cytochrome P450 3A4*22, PPAR-α, and ARNT polymorphisms and clopidogrel response. *Clin. Pharmacol.* **5**, 185–192 (2013).
26. European Medicines Agency (EMA) Guideline on the use of pharmacogenetic methodologies in the pharmacokinetic evaluation of medicinal products <https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-use-pharmacogenetic-methodologies-pharmacokinetic-evaluation-medicinal-products_en.pdf> (2012). Accessed February 19, 2020.
27. Maliepaard, M. *et al.* Pharmacogenetics in the evaluation of new drugs: a multiregional regulatory perspective. *Nat. Rev. Drug Discov.* **12**, 103–115 (2013).
28. European Medicines Agency (EMA) Guideline on the investigation of drug interactions CPMP/EWP/560/95/Rev. 1 <https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-drug-interactions_en.pdf> (2012). Accessed February 19, 2020.
29. European Medicines Agency (EMA) Guideline on the investigation of bioequivalence <https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-bioequivalence-rev1_en.pdf> (2010). Accessed February 19, 2020.
30. Williams, J.A. *et al.* Comparative metabolic capabilities of CYP3A4, CYP3A5, and CYP3A7. *Drug Metab. Dispos.* **30**, 883–891 (2002).
31. DiMasi, J.A., Hansen, R.W. & Grabowski, H.G. The price of innovation: new estimates of drug development costs. *J. Health Econ.* **22**, 151–185 (2003).
32. Spector, J.M., Harrison, R.S. & Fishman, M.C. Fundamental science behind today's important medicines. *Sci. Transl. Med.* **10**, 1–5 (2018).