Regulatory Aspects of Pharmacogenomics in Clinical Drug Development

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1 Summary

Pharmacogenomics promises to revolutionise medicine with better defined dosing, identification of poor responders and identification of patients likely to develop adverse drug reactions. This is often referred to as a move to personalised medicine. To fulfil this promise pharmacogenomics has to be included in drug development programmes. Except for certain pharmacokinetic studies, there are few regulatory requirements to include pharmacogenomics into clinical trials. Sponsors, considering whether to include pharmacogenomics on a voluntary basis, have to understand the regulatory implications for the approval of the drug. This thesis discusses the criteria that may be considered when integrating pharmacogenomics into drug development programmes and assesses the regulatory implications.

In healthy volunteer Phase 1 pharmacokinetic studies and drug interaction studies, genotyping is mandated by the relevant guidelines if a drug is known to be predominately metabolised by one enzyme. The influence of genetic polymorphisms on drug metabolising enzymes of the CYP family is well established, and a number of validated tests are available. The influence of other metabolising or transporting systems is less well understood, and validated tests may not be available. In this case tests for these markers may be included in Phase 1 studies on an exploratory basis. Based on the Phase 1 results, genotyping may be continued into patient studies to further characterise the relationship between genotype and pharmacokinetics, genotype and pharmacodynamics and, ultimately, to predict drug response. The genetic aspects of pharmacokinetic variability may be translated into warnings in the SPC. As yet, there are very few examples where genotyping is recommended before dosing.

The decision to include pharmacogenomics in Phase 2/3 efficacy and safety studies may be based on several factors including the type of disease, the level of knowledge on the genetic involvement in primary or secondary pharmacodynamics and the availability and validity of the genomic tests. Depending on the validity of the genomic biomarkers, pharmacogenomics in safety and efficacy studies may be used for patient selection, as part of the confirmatory analysis, as part of the supporting analyses or in an exploratory fashion. Accordingly, the results may be reflected in different parts of the SPC, or may not be reflected at all.

When developing drugs for severe diseases with a clear monogenetic component to the mechanism of drug action (e.g. targeted cancer therapy drugs), the inclusion of pharmacogenomics seems obvious. Severe adverse events in a small number of patients may also lead to exploring pharmacogenomics. Here, excluding patients at risk may make the drug viable without significantly restricting the patient population.

When dealing with less severe diseases and adverse events, there is less incentive to study pharmacogenomics. For example, the identification of subgroups who are less likely to respond may restrict the market potential of the new drug. However, most

pharmacodynamic drug effects are polygenetic in nature, and in most cases pharmacogenomics will merely provide different levels of risk (response or adverse reactions), but will not result in label restrictions.

Both, FDA and EMEA, encourage the integration of pharmacogenomics into clinical development programmes, including the use of exploratory markers that are unlikely to be used for regulatory decision making. To facilitate communication between the pharmaceutical industry and regulators, both agencies have established processes by which sponsors can submit and discuss pharmacogenomic plans and data. Joint meetings with both agencies are also possible.

In both regulatory territories all relevant information has to be submitted as part of submissions for new drugs. In the context of genomic data, FDA provides clear guidance on timing and format of mandatory and voluntary genomic data submissions. The main criteria for these submissions are the validity of the biomarkers and the intended use in label claims.

At this point, most pharmacogenomic tests are exploratory, and it is up to the pharmaceutical companies to include these in their clinical development programmes. Advantages may include better characterised drugs with clearer defined patient populations, more precise dosing and less adverse reactions. The disadvantages may include increased development costs, mandated genomic tests and restricted patient populations. The uptake of pharmacogenomics may be slow, but as science progresses and the regulatory requirements become clearer, pharmacogenomics is likely to become an integral part of drug development.

2 List of Abbreviations

Term	Meaning
AE	adverse event
AUC	area under the curve
BLA	Biologics License Application (US)
CFR	Code of Federal Regulations (US)
CHMP	Committee for Human Medicinal Products, formerly CPMP (EU)
CIOMS	Council for International Organisations of Medicinal Sciences
CPMP	Committee for Proprietary Medicinal Products, renamed to CHMP (EU)
CYP	cytochrome P450, a diverse family of hemoproteins involved in the metabolism of drugs and xenobiotics
EM	extensive metaboliser
EMEA	European Medicines Agency (EU)
EPAR	European Public Assessment Report
FDA	Food and Drug Administration (US)
HER-2	a member of the epidermal growth factor receptor family
HHS	Department of Health and Human Services (US)
HSR	hypersensitivity reaction
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDE	Investigational Device Exemption (US)
IND	Investigational New Drug Application (US)
IPRG	Interdisciplinary Pharmacogenomics Review Group at FDA (US)
NDA	New Drug Application (US)
OATP	organic anion transporter protein
PD	pharmacodynamics
PG	pharmacogenomics
P-gp	p-glycoprotein

PGWG	Pharmacogenetics Working Group established by CHMP (EU)
PK	pharmacokinetics
PM	poor metaboliser
SPC	Summary of Product Characteristics (EU)
VGDS	Voluntary Genomic Data Submission (US)
WHO	World Health Organisation

"If it were not for the great variability among individuals, medicine might well be a science and not an art"

Sir William Osler 1892

3 Introduction

Pharmacogenomics, the use of genomic techniques in the study of pharmacological function, drug disposition and drug action, will allow a better understanding of drug response on an individual level. This is the main basis for a move towards a more individualised medicine, which is commonly referred to as personalised medicine. To better describe the concept of using pharmacogenomics to identify subgroups (rather than individuals), a recent paper introduces the term stratified medicine.[1]

The term pharmacogenetics, first introduced in 1959[2], has been used to describe a scientific discipline that deals with genetic differences in the response to drugs. With the transition from genetics to genomics (the global analysis of genotypes) the term pharmacogenomics has been introduced. This term is understood to broadly cover the use of genomic techniques in the study of pharmacological function, drug disposition and drug response. Sometimes the terms pharmacogenetics and pharmacogenomics are used interchangeably. The terminology used in regulatory documents will be discussed in section 4. However, throughout this thesis the term pharmacogenomics will be used to broadly cover the use of genetic or genomic techniques in the study of drug response. The term pharmacogenetics will be used when the genetic information is limited to the DNA sequence.

The genetics of a number of drug metabolising enzymes involve polymorphisms of single genes. The influence of these polymorphisms on pharmacokinetics is well understood and the regulatory requirements in this area have evolved over time. In contrast, the prospect of studying pharmacogenomics of complex genetic traits (multi-gene involvement, whole genome sequencing, gene expression profiles) is quite recent. Following the human genome project in 2000, new genomic techniques have become available and the costs of these have dropped dramatically. This trend is certain to continue. The US National Human Genome Research Institute (NHGRI) launched a 10 year programme aimed at reducing the cost of sequencing a mammalian genome to $ 1000.[3]

The excitement about the new prospects in pharmacogenomics is matched by some reluctance by the pharmaceutical industry to adopt pharmacogenomics in their drug development. Among the reasons for this may be that the regulatory requirements are not clearly defined at present. For example, in the March 2004 FDA white paper *Stagnation or Innovation? Challenge and Opportunity on the Critical Path to New Medicinal*

Products,[4] pharmacogenomics was identified as a key critical path opportunity. FDA also states that "emerging techniques of pharmacogenomics and proteomics show great promise for contributing biomarkers to target responders, monitor clinical response, and serve as biomarkers of drug effectiveness. However, much development work and standardisation of the biological, statistical and bioinformatic methods must occur before these techniques can be easily and widely used."

Pharmacogenomics has the potential to personalise medicine in the following 3 aspects: better defined dosing, identification of subgroups that are more likely or less likely to respond and identification of subgroups that are more prone to adverse drug reactions. These aspects are linked to pharmacokinetics, primary pharmacodynamics and secondary pharmacodynamics, respectively. Therefore the study of these aspects during clinical development requires different approaches, some of which have become standard (drug metabolising enzymes) while others are still exploratory. From a public health point of view it is obviously desirable to incorporate pharmacogenomics in clinical development programmes to optimise prescription information and drug use.

There are several examples where clinically relevant variability in drug action has been linked to genetic factors after the drug had been approved and marketed, sometimes for several decades. Well known examples include Warfarin, Codeine, Thiopurines, Phenytoin, which show variability in pharmacokinetics based on polymorphisms of metabolising enzymes. Post approval experience and retrospective studies have resulted in labelling changes of these products.[5, 6]

A number of drugs have been withdrawn from the market because of uncommon, but severe adverse reactions. It is believed that, at least for some drugs, genetic disposition may be the reason for these rare events.[7] It is conceivable that some of these drugs could still be on the market if genomic tests to detect the genetic disposition for adverse reactions had been available.

Drugs that have shown high variability in pharmacodynamic or adverse drug effects during the marketing phase may have been developed before pharmacogenomics was used in drug development or even before pharmacogenomics existed. Today, a large number of genomic tests, some validated, most exploratory, are available. Drug developers have to consider if and when to include pharmacogenomics in their clinical programmes. Data generated at the beginning of clinical development may be submitted 6 or even 10 years later. Therefore, it is important to anticipate how the scientific and regulatory environment will change over time.

Integration of pharmacogenomics in drug development by pharmaceutical companies has been rather slow. Reasons for this may include the uncertainty connected with using exploratory biomarkers and the increased development cost. There is also the fear that the current business model of "one drug fits all" may be threatened by personalising medicine. The regulatory requirements are not yet well defined and the regulatory

implications, once pharmacogenomic data have been generated, are also uncertain. However, over the last few years regulatory agencies have started to encourage the integration of pharmacogenomics into drug development. At the same time, regulatory frameworks to support pharmacogenomics are being developed.

The aim of this thesis is to review the current status of pharmacogenomics in clinical drug development and to discuss the evolving regulatory environment in the US and the EU. The thesis intends to provide criteria to be considered when integrating pharmacogenomics in clinical trials. Possible labelling implications are also discussed.

4 Definitions in Pharmacogenomics

Pharmacogenomics is a rapidly evolving field in medical science and the terminology is still being defined. When considering the inclusion of pharmacogenomics into global drug development projects, it is important to understand the terminology used in the scientific literature and regulatory documents.

Pharmacogenetics versus Pharmacogenomics

Since its first introduction in 1959,[2] the term pharmacogenetics has been used in the scientific literature to describe inherited genetic differences in drug response. Until the 1980s the study of genetic differences was mainly limited to differences in DNA sequences. With the advent of genomic techniques (such as, molecular genetics, cloning, whole genome sequencing, expression profiling) the term pharmacogenomics has evolved. It encompasses the use of any of the genomic techniques in drug discovery, study of pharmacological function, drug disposition and therapeutic response.

Over the last few years, regulatory bodies have tried to define the terms pharmacogenetics and pharmacogenomics in a number of guidelines. In the 2003 EMEA *Position Paper on Terminology in Pharmacogenetics*,[8] pharmacogenetics is defined as "the study of interindividual variations in DNA sequence related to drug response". On the other hand, pharmacogenomics is defined as "the study of the variability of the expression of individual genes relevant to disease susceptibility as well as drug response at cellular, tissue, individual or population level. The term is broadly applicable to drug design, discovery, and clinical development".

In the 2005 Guidance for Industry on *Pharmacogenomics Data Submissions*,[9] FDA states that the term pharmacogenomics is defined as "the use of a pharmacogenomic or pharmacogenetic test in conjunction with drug therapy". A pharmacogenetic test is defined as "an assay intended to study interindividual variations in DNA sequence related to drug absorption and disposition (PK) or drug action (PD) including polymorphic variation in the genes that encode the functions of transporters, metabolising enzymes,

receptors and other proteins". A pharmacogenomic test is defined as "an assay intended to study interindividual variations in whole-genome or candidate gene, single-nucleotide polymorphism (SNP) maps, haplotype markers, or alterations in gene expression or inactivation that may be correlated with pharmacological function and therapeutic response. In some cases the *pattern or profile of change* is the relevant biomarker, rather than changes in individual markers". Therefore, the guideline uses the term pharmacogenomics throughout, whether the underlying information is pharmacogenetic (DNA sequence) or pharmacogenomic (any genetic characteristic) in nature.

In a most recent (2006) ICH document, *Note for Guidance on Establishing Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories,*[10] pharmacogenomics is defined as "the investigation of variations of DNA and RNA characteristics as related to drug response". Pharmacogenetis is classified as a subset of pharmacogenomics and is defined as "the influence of variation in DNA sequence on drug response". According to these concise definitions, the difference between pharmacogenomics and pharmacogenetics is that the latter is limited to DNA sequence information. Pharmacogenomics includes any genomic information in relation to drug response. The note for guidance is currently at step 3 of the ICH process, and the deadline for comments was in February 2007. It remains to be seen how the terms are defined at the end of the ICH process. However, once agreed, the ICH definitions are likely to become the accepted definitions world wide.

In line with the ICH proposals, this thesis will use the term pharmacogenomics in the broad sense to cover the use of genetic and genomic techniques in the study of drug response. The term pharmacogenetics will be used when the genetic information is limited to the DNA sequence.

Genetic Testing versus Pharmacogenomic Testing

The term genetic testing is used to describe clinical tests that link genetic characteristics to the development of disease. Genetic testing aims at predicting the likelihood of disease occurring. Pharmacogenomic testing links genetic characteristics to likely drug response. Pharmacogenomic testing is intended to provide information that may be used to choose a therapeutic and/or its dosage.[11]

Genetic testing is used in subjects who are suspected of having or are at risk of developing a particular disease or condition. Pharmacogenomic testing is used after the disease has occurred to predict likely drug response.[11] In future, genomic data may be collected and stored. The data would then be used for various purposes when needed. In this scenario, the distinction between genetic and pharmacogenomic testing would become less clear.

The use of genetic testing in drug development and the related regulatory aspects are not within the scope of this thesis.

Genotyping versus Phenotyping

The genotype is all or part of the genetic constitution of an organism. The genotype is laid down in physical DNA molecules and is inherited. The phenotype describes the observable properties of an organism that are produced by the interaction of the genotype and the environment.[12] The aim of pharmacogenomics is to correlate genotypes and phenotypes which are relevant to drug response. Good examples for established correlations between genotypes and phenotypes are some of the drug metabolising enzymes, such as CYP2D6. Here genotype can be elucidated by studying the phenotype using model substances as metabolic probes (e.g. dextromethorphan).[7] At the same time phenotype can be reliably predicted by genotyping. However, for most other mechanisms that influence pharmacokinetics and for most pharmacological targets such correlations are not known at present.

Phenotypical effects that are typically studied in clinical trials are shown in the following table together with possible genotypical variables.

	Pharmaco-kinetics	**Primary Pharmacodynamics**	**Secondary Pharmacodynamics**
typical **phenotype** effects	plasma levels	efficacy	safety
examples of **genotype** variables	metabolising enzymes (e.g. CYPs) transporters (e.g. pGP, OATP)	drug targets (e.g. receptors for growth factors)	immune response systems (e.g. HLA-B*5701) channels (e.g. HERG)

Genomic Biomarkers

A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic response to a therapeutic intervention.[13] Biomarkers are widely used in medicine, and examples of commonly used biomarkers include blood pressure and blood cholesterol levels.

Biomarkers are useful when they correlate with patient relevant parameters, such as time to onset of disease, life time or disease free time. Ideally, they link effects on single markers to single medical effects (blood pressure to heart attack).

In the context of pharmacogenomics, genomic biomarkers are used to relate genomic information to drug response. Genomic biomarkers with single marker to single effect relationships include some of the CYP enzymes and certain genes in somatic cancer cells (e.g. Her-2).

An important characteristic of a biomarker is its validity. According to the FDA Guidance for Industry on *Voluntary Genomic Data Submissions*,[9] a biomarker is valid if it is "measured in an analytical test system with well established performance characteristics and for which there is an established scientific framework or body of evidence that elucidates the physiologic, toxicologic, pharmacologic, or clinical significance of the test results". The guideline further defines a known valid biomarker for which there is "widespread agreement in the medical or scientific community about the physiologic, toxicologic, pharmacologic, or clinical significance of the results." For a probable valid biomarker there is "a scientific framework or body of evidence that appears to elucidate the physiologic, toxicologic, pharmacologic, or clinical significance of the test results". A probable valid biomarker may not have "reached the status of a known valid biomarker because the data, although highly suggestive of significance, may not be conclusive". It is also worth noting that the validity of a biomarker is context specific and depends on its intended use.

In the field of pharmacogenomics only a few biomarkers are considered valid, while the vast majority is still in an exploratory state. A *Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels* can be found on the FDA website.[14]

5 Pharmacogenomics in Phase 1 Pharmacokinetic Studies

The objective of a pharmacokinetic (PK) programme is to investigate the fate of a drug in the human body and to identify any factors that may influence it. These include extrinsic factors (such as food interactions, tobacco, alcohol) and intrinsic factors (such as age, sex, body weight). Among the important intrinsic factors is the genetic makeup.

The study of pharmacokinetics includes absorption, distribution, metabolism, and elimination. All of these aspects may be influenced by genetic factors. However, clinically relevant effects are best documented in the area of drug metabolism. The most important class of drug metabolising enzymes in this context is the cytochrome P450 family (CYP). Polymorphisms have been identified for most of the CYP enzymes. They have been studied extensively, but their validity as biomarkers is variable. However,

CYP2D6 and CYP2C19 are considered valid biomarkers, and in 2005 FDA approved Roche's AmpliChip® for measuring polymorphisms of these 2 enzymes.[15]

Polymorphisms of drug metabolising enzymes may give rise to different phenotypes which are generally divided into 4 groups, poor metabolisers, intermediate metabolisers, extensive metabolisers and ultra-rapid metabolisers (table below).[16] Often the majority of the population falls into the category of extensive metabolisers; hence, they are also described as "normal" metabolisers. Genotypically, extensive metabolisers are characterised by the presence of 2 functional alleles for the metabolising enzyme.

	Genotype	**Phenotype**
Poor Metaboliser	no functional allele	lack of functional enzyme; metabolism using different route
Intermediate Metaboliser	one functional allele and one deficient allele or two partly deficient alleles	metabolism may be reduced
Extensive Metaboliser	two functional alleles	"normal" metaboliser
Ultra-rapid Metaboliser	duplicated allele or multiduplicated functional alleles	extremely high metabolic capacity

Depending on the type of drug, differences in metabolism may increase or decrease exposure to the active substance. If an active drug is inactivated by metabolism, slow metabolism will increase exposure. If a drug is a prodrug that needs to be metabolised to form the active substance, slow metabolism will decrease exposure. The table below shows some of the possible consequences.[16]

Drug	Slow Metaboliser	Fast Metaboliser
Active drug **(e.g. warfarin)**	good efficacy accumulation of active drug can produce adverse reaction lower dose may be needed	poor efficacy greater dose or slow release formulation may be needed
Prodrug **(e.g. codeine)**	poor efficacy possible accumulation of prodrug	good efficacy rapid effect

Differences in metabolism may also affect drug drug interactions. For example, ultra-rapid metabolisers may not show the same level of drug drug interaction as extensive metabolisers. Poor metabolisers (who have no functional allele) do not show drug interactions predicted from *in vitro* studies.

In addition to the well characterised metabolic enzymes, there will be other genetic characteristics that can influence pharmacokinetics. It should be considered whether to investigate any exploratory genomic variables as part of the pharmacokinetic programme, in particular, if unexpected variability is observed.

Using pharmacogenomics in pharmacokinetic studies may yield genotype phenotype relationships that lead to identifying populations of patients with better safety profiles, better efficacy rates and/or need for different dosage regimes.

5.1 Drug Metabolism Studies

As part of a standard preclinical development programme metabolism is investigated in *in vitro* studies. If the *in vitro* screening tests show that the drug is mainly metabolised by one system only, *in vivo* studies with appropriately genotyped and/or phenotyped subjects are generally required. Other factors to be considered include the therapeutic dose range and the severity of the disease. Ethnic differences in the genetic distribution of the main metabolising enzymes should also be considered, in particular, if the acceptability of foreign clinical data is important.[17]

As early as 1987 genetic differences were mentioned in the EU *Notice to Applicants*[18] as one of the factors to be considered in pharmacokinetic studies: “Other factors like body weight, time of day, environmental factors, genetic differences, alcohol, smoking habits, concomitant medication, sex, may markedly interfere, and if there is particular reason to

believe that these may markedly influence the results and the interpretation of later clinical studies, kinetic studies should be extended accordingly".

The 1999 FDA Guidance to Industry on *In Vivo Drug Metabolism/Drug Interaction Studies*[19] states that "identifying metabolic differences in patient groups based on genetic polymorphism, or on other readily identifiable factors, such as age, race, and gender can aid in interpreting the results". And further it states that "in either patient or healthy/general population subject studies, performance of phenotype or genotype determinations to identify genetically determined metabolic polymorphisms is often important in evaluating effects on enzymes with polymorphisms, notably CYP2D6 and CYP2C19".

The 2002 CHMP *Note for Guidance on the Investigation of Bioavailability and Bioequivalence*[20] states that "phenotyping and/or genotyping of subjects should be considered for exploratory bioavailability studies and all studies using parallel group design. It may be considered as well in crossover studies (e.g. bioequivalence, dose proportionality, food interaction studies etc.) for safety or pharmacokinetic reasons. If a drug is known to be subject to major genetic polymorphism, studies could be performed in panels of subjects of known phenotype or genotype for the polymorphism in question."

The above guidelines focus on the inclusion of genotyping and/or phenotyping in Phase 1 studies. The use of genotyping in later phases is not specifically mentioned, and details on study design and labelling implications are not given in the guidance. However, the intention is the characterisation of subgroups which would receive different exposure to the drug and may show different safety profiles. The regulatory frame work is still evolving, but the current thinking in this area may be gauged from a most recent (May 2007) EMEA *Reflection Paper on Pharmacogenomics in Pharmacokinetics*,[21] which will be discussed below.

The reflection paper states that "studies of the effect of pharmacogenetics on pharmaco-kinetics are required for pharmacokinetic evaluation of a new chemical entity if the genetic variation is likely to translate into important differences in the systemic and/or local exposure to this substance or its active or toxic metabolites, thereby potentially affecting safety and efficacy of the treatment". While pharmacogenetic studies for active substances with these characteristics have been mentioned in the earlier guidelines, the inclusion of active and toxic metabolites in pharmacogenetic studies may considerably expand the scope of the pharmacokinetic studies.

In addition, the reflection paper states that "combined pharmacogenetic/pharmacokinetic studies that may contribute to the identification of novel polymorphic loci are encouraged if the compound exhibits important inter-individual pharmacokinetic variability, likely to affect clinical efficacy and/or safety". Studying pharmacogenetics if there are no evident genetic explanations, could mean studying a large number of possible target genes that

may be involved in metabolism or transport of the drug. However, the paper does not cover pharmacogenomics as a means to study pharmacokinetic variability.

The paper also states that "when the involvement of the polymorphic gene has been verified, *in vivo* studies of the effects of specific polymorphisms on the pharmacokinetics of the pharmacologically active compounds likely to contribute to clinical efficacy and/or safety are recommended". Therefore, Phase 1 studies with genetically preselected subjects should be conducted to study the effect of different genotypes. In addition, genotyping is encouraged in as many of the Phase 1, 2 and 3 clinical studies as possible to increase the amount of data supporting the recommendations for use in genetic subpopulations. The paper states that "dose-response 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".

The requirements are not well defined yet and have to be evaluated by the drug developer on a case by case basis. However, pharmacogenetics should be considered an integral part of the clinical study programme. This will allow the evaluation of the clinical consequences of genetic differences in drug substance exposure. When deciding on the extend of pharmacogenetics during the programme, the properties of the drug and type of disease should be considered: e.g. the safety margin, the severity of disease and adverse reactions, pharmacodynamic curve for both efficacy and safety. For drugs with a narrow safety margin or a steep pharmacodynamic curve, the inclusion of pharmacogenetics is more important. However, these factors are generally not well understood at the beginning of development.

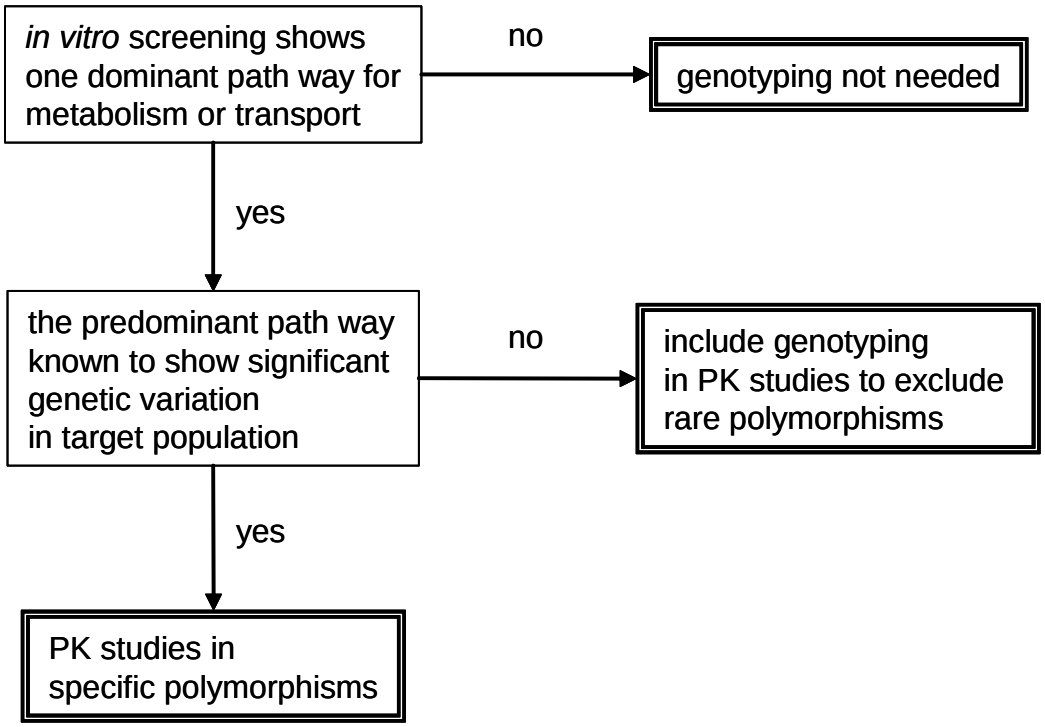
The paper recommends to store samples from early Phase 1 studies "to allow retrospective analyses when more experience has been gained or new proteins have been shown to play a major role in the pharmacokinetics of the active substances". Scientifically, this recommendation seems justified, but it is likely to create practical and ethical problems. Due to regulatory restrictions and lack of patient consent it may become difficult to carry out Phase 1 studies in some countries.

With regards to the consequences of genetic differences, the paper concludes that, if significant differences between genetically defined subpopulations are observed, this could have implications on dose recommendations and labelling. Where applicable, differences may still be managed by titration. However, it may become necessary to have different dosing recommendations based on phenotype and/or genotype. Where suitable doses cannot be recommended warnings or contraindications may be appropriate.

Despite the advances in genomics the focus in the area of pharmacokinetics remains on genetic variation of the DNA sequence. The EMEA *Reflection Paper on Pharmacogenetics in Pharmacokinetics* states that "the broader issue of pharmacogenomics (PGx), i.e. the variability in the entire genome relevant to drug response, will not be considered".[21]

In conclusion, this thesis proposes the following decision tree for the integration of pharmacogenetics into pharmacokinetics studies (Figure 1). It is worth noting that the decision tree should not be used in isolation; other factors, such as type of disease, expected consequences of over/under- dosing, ethnic differences, should also be considered. However, the main criterion for inclusion of genotyping in pharmacokinetic studies is *in vitro* studies indicating a dominant path way for metabolism or transport.

Figure 1 Integration of Pharmacogenetics into Pharmacokinetic Studies



5.2 Drug Drug Interaction Studies

Drug drug interaction may be caused by competition for, inhibition of or induction of metabolic enzymes or transporters. The role of pharmacogenomics in drug drug interaction studies is to ensure that appropriate subjects are included in these studies. Even if polymorphisms of metabolising enzymes did not show significant effects in standard pharmacokinetic studies, drug drug interaction could be affected dramatically. For example, poor metabolisers may not show any effect since this path way cannot be inhibited. On the other hand, ultra-fast metabolisers may not show any effect since this path way cannot be overloaded with substrate.

The 1997 EMEA *Note for Guidance on the Investigation of Drug Interactions*[22] states that "subjects participating in metabolic *in vivo* interaction studies should be appropriately genotyped and/or phenotyped if any of the active enzymes mediating the metabolism are polymorphically distributed in the population. In some cases, clinically relevant interactions may only occur in a subset of the total population, for instance, slow metabolisers, when an alternative route of metabolism is inhibited."

The 1999 FDA Guidance to Industry on *In Vivo Drug Metabolism/Drug Interaction Studies*[19] contains a statement that "in either patient or healthy/general population subject studies, performance of phenotype or genotype determinations to identify genetically determined metabolic polymorphisms is often important in evaluating effects on enzymes with polymorphisms, notably CYP2D6 and CYP2C19".

The 2006 FDA draft Guidance to Industry on *Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labelling*[23] develops these concepts further, and it contains 2 relevant paragraphs on genotyping study subjects: "Performance of phenotype or genotype determinations to identify genetically determined metabolic polymorphisms is important in evaluating effects on enzymes with polymorphisms, notably CYP2D6, CYP2C19 and CYP2C9. The extent of drug interactions (inhibition or induction) may be different depending on the subjects' genotype for the specific enzyme being evaluated. Subjects lacking the major clearance pathway, for example, cannot show metabolism, and remaining pathways can become important and should be understood and examined". The guideline continues: "Identifying metabolic differences in patient groups based on genetic polymorphism, or on other readily identifiable factors, such as age, race and gender can aid in interpreting results. The extend of interactions may be defined by these variables (e.g. CYP2D6 genotypes). Further, in subjects who lack the major clearance pathway, remaining pathways become important and should be understood and examined".

The guideline also contains lists of known substrates, inducers and inhibitors for a number of known enzymes and transporters. For up-to-date lists the guidelines refers to the FDA drug interaction website.[24]

The recent (2007) EMEA *Reflection Paper on Pharmacogenetics in the Pharmacokinetic Evaluation of Medicinal Products*[21] states that "genotyping of the population included in an interaction study is recommended when pharmacogenetics is expected to affect the pharmacokinetics of any of the active substances. Depending on the question investigated, directed inclusion or exclusion of specific genotypes may be useful."

The existing guidelines on drug drug interactions are limited to metabolising enzymes and to some transporters. As science evolves, additional genes, including those for pharmacodynamic targets, may be used in drug drug interaction studies. Even now, the use of exploratory pharmacogenomic markers should be considered if clinically relevant, unexpected interaction effects are observed.

6 Pharmacogenomics in Phase 2/3 Efficacy and Safety Studies

There may be various reasons for collecting pharmacogenomic data during Phase 2/3 efficacy and safety studies. Depending on the results of the Phase 1 pharmacokinetic programme, it may be necessary to further investigate the pharmacogenomic / pharmaco-kinetic relationship in patients and to link these data with safety and efficacy results (section 6.1). Where genetic factors are known or suspected to be involved in the mechanism of action it may be necessary or advisable to collect pharmacogenomic data in Phase 2/3 patient studies (section 6.2). Depending on the type of disease, level of knowledge on the genetic involvement in primary or secondary pharmacodynamics and the availability of validated biomarkers, pharmacogenomic data may be used for patient selection and/ or part of the confirmatory analyses (section 6.2.1). Where the genomic biomarkers are not suitable to be included in the main analysis, pharmacogenomic data may be collected for auxiliary (secondary) analyses or for purely exploratory analyses to generate new hypothesis (section 6.2.2).

6.1 Pharmacokinetics Related Genomic Data Collection

If Phase 1 pharmacokinetics studies have shown that the pharmacokinetics of a drug are variable because of genetic factors it becomes indispensable to collect pharmacogenomic data in patients during the Phase 2/3 safety and efficacy trials. Assuming that the involved genes are known valid biomarkers, patients may be pre-selected based on genotype. This will ensure that an appropriate number of patients are included in each sub-group. Alternatively, patients may be genetically classified for planned post hoc analyses.

Strattera® (atomoxetine) may be used to illustrate how pharmacogenomic data collected during development are used to define dosing.[25] Strattera® was approved by FDA in July 2003 for attention deficit hyperactive disorder. Atomoxetine is primarily cleared by CYP2D6 with plasma clearance of 0.35 L/hr/kg in EMs and 0.03 L/hr/kg in PMs. The

observed area under the curve (AUC) ratio for PMs/EMs was 10. The AUC in PMs was similar to the AUC observed in EMs with concomitant administration of CYP2D6 inhibitors. The applicant collected pharmacogenetic data in all efficacy and safety studies. In some studies only EMs were allowed to enrol.

During the review, FDA assessed whether the recommended dose should be "individualized" based on genotype. The pharmacogenetic data base collected during the safety and efficacy trials allowed a retrospective analysis of subsets based on genotype. The analysis showed adverse event rates of 9% in PMs and 6% in EMs. Discontinuation because of adverse events was 3.5% in PMs and 1.5% in EMs . There were no major differences in serious AEs between PMs and EMs.

One aspect discussed during the review was the definition of PM. One group of patients was defined as PM based on their genotype. Another group (who did not have the PM-genotype) was considered PM based on their phenotype, because of concomitant administration of CYP2D6 inhibitors. In their retrospective subgroup analysis, the sponsor combined the 2 groups based on the phenotype. However, FDA considered these two groups separately.

In the end, FDA did not recommend dose reduction of the genetically defined PMs and, hence, does not require a pharmacogenomic test before prescription. However, for the phenotypically defined PMs (co-administration of CYP2D6 inhibitors) dose reduction was recommended and can be found in the product label.

Considering that similar increases in plasma levels were observed for genetically defined PMs and for phenotypically defined PMs, this decision may seem surprising. Among the reasons why genotyping was not mandated before prescribing Strattera® is that the dose is individually titrated to achieve the desired clinical effect.

Other factors contributing to the decision not to include genotype in the dosing recommendations may be the definition of PM in this context. There are more than 40 alleles of CYP2D6, of which about 10 alleles having greatly decreased or null activity. The label could refer to specific alleles or just an overall genotype (PM, EM). In addition there may have been concerns regarding the availability, cost and quality of CYP2D6 tests.[26]

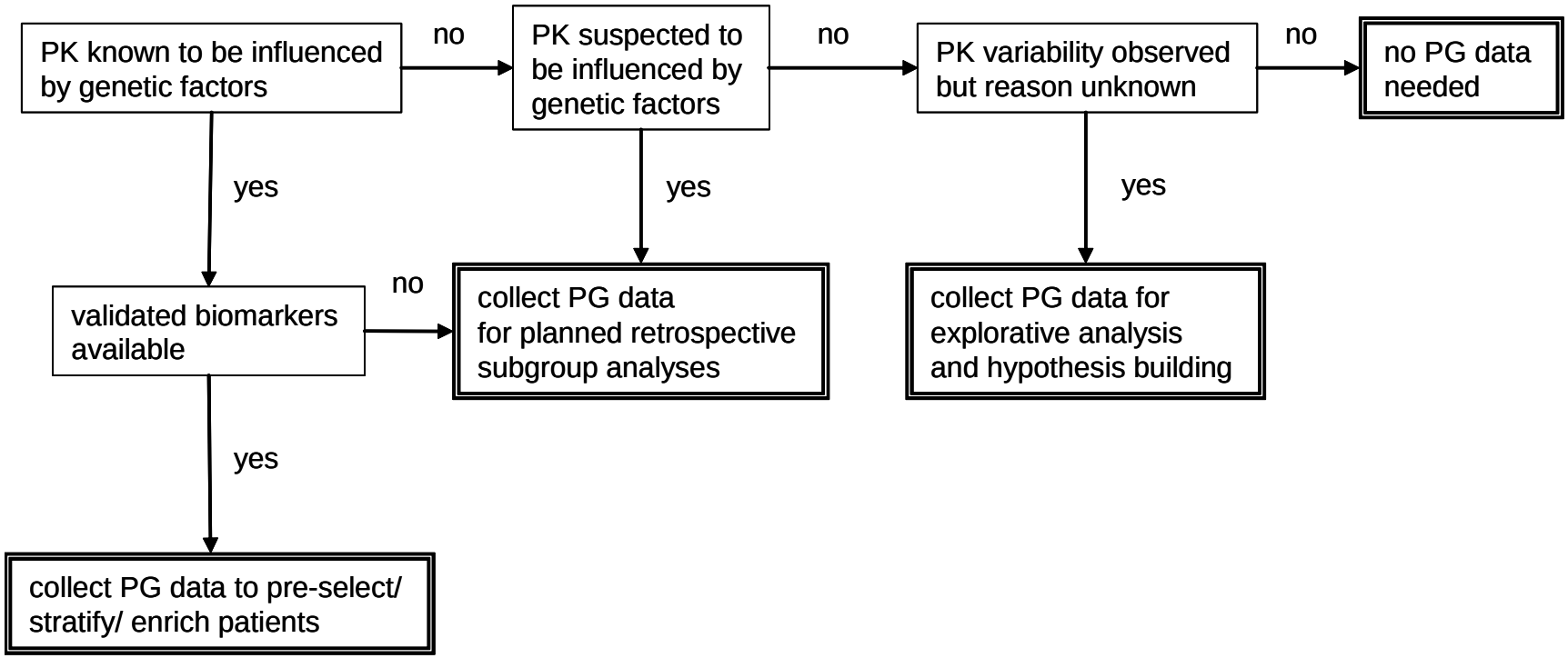
Presumably, it was also felt not practicable to mandate a pharmacogenomic test before prescribing Strattera®. Since approval of Strattera®, FDA has approved Roche's AmpliChip® CYP450 test for the rapid genotyping of CYP2D6 and CYP2C19 .[15] It seems just a matter of time when genotyping will be recommended for products like Strattera®.

The Strattera® example shows that, when developing a new drug, whose pharmacokinetics are known or suspected to be influenced by genetic factors, it will be important to generate a solid pharmacogenomic data base during safety and efficacy

trials. Depending on the availability of validated biomarkers, it may be necessary to generate sufficient data in genotypically defined subpopulations. The aim of these studies is to further characterise the genotype phenotype relationship. Phenotype may be defined in terms of pharmacokinetic and/or pharmacodynamic parameters.

In conclusion, this thesis proposes the following decision tree to define the integration of pharmacokinetics related pharmacogenomics into Phase 2/3 safety and efficacy trials (Figure 2). It should be noted that other factors (such as type of disease, shape of dose response curve) should also be considered. However, where pharmacokinetics are known to be influenced by genetic factors and where validated biomarkers are available, it should be considered to preselect certain genotypes or to stratify for certain genotypes. Where these conditions are not met, collection of genomic data should be considered for planned retrospective analyses or for possible exploratory analyses.

Figure 2 Pharmacokinetics Related Pharmacogenomics Data Collection in Phase 2/3 Safety and Efficacy Studies



6.2 Pharmacodynamic Related Genomic Data Collection

6.2.1 Confirmatory Endpoints

For some drugs there may be sufficient knowledge on the genetic aspects of the mechanism of action to include pharmacogenomics in the main analysis of clinical trials or to preselect patients based on their genetic disposition. Other drugs are developed to specifically aim at targets that are known to be linked to genetic traits. In particular in targeted cancer therapy, genetic abnormalities of cancer cells are exploited to achieve therapeutic effects. When developing such an agent, preclinical *in vitro* and *in vivo* studies will be used to demonstrate the feasibility of the mechanism of action, before the start of confirmatory clinical studies.

When starting clinical trials in patients, it has to be considered whether or not to select patients based on genetic tests and, if so, how. The relevant genetic trait may be the presence or absence of a particular gene, which can be used as a determining factor. Where the level of overexpression of a gene is the determining factor, an appropriate cut off level for the overexpression needs to be defined for the preselection of patients. This further complicates the trial design, since the appropriate cut-off level is generally not known at the beginning of the trial. Different levels of overexpression may also be used as secondary variables in the analysis of the study (see 6.2.2). In any case, the validity of the biomarker (testing method and validity in the clinical context) used in confirmatory studies should be considered carefully.

When using genetically based patient selection during drug development this will be reflected in the indication. The availability and validity of the test has to be considered, both during the clinical trials and after approval. FDA states that such a drug can only be approved if a validated assay is available.[9] If necessary, the sponsor should consider co-development of drug and test, for which a draft FDA guideline is available.[27] It can be assumed that a valid test will also be required for approval in the EU.

Herceptin® (trastuzumab) may be used to illustrate the development of a targeted cancer drug using a genomic test[a] for patient selection.[28] The human epidermal growth factor receptor gene expression (HER-2) is amplified in up to 30% of patients with breast cancer,

[a] It may be worth noting that during development, overexpression of HER-2 receptor was measured directly by immunohistochemistry which may be considered a phenotype test. Subsequently, genomic tests (FISH, CISH) that measure the amplification of the HER-2 gene itself, have been validated and have been included in the SPC.

resulting in the overexpression of the HER-2 receptor, which serves as the target for the anti-HER-2 antibody trastuzumab.

In clinical trials patients were prospectively selected based on overexpression of the HER-2 receptor. Only patients with 2+ and 3+ levels were allowed into the study. The pivotal studies were not designed to allow sub group analysis of patients expressing HER-2 at 2+ or 3+ level, and no stratification at randomisation on the basis of level of overexpression was performed. Based on the evidence of efficacy shown for the whole patient group the product was approved. However, in the scientific discussion there was some concern over the lack of correlation between clinical benefit and the HER-2 expression level.

Following the genomically defined inclusion criteria during clinical development, the indication is limited to "patients with overexpression". Therefore testing of the HER-2 status is required before prescribing trastuzumab.

The development of Herceptin® may be compared with that of Tarceva® (erlotinib),[29] another targeted cancer drug. Erlotinib targets the human epidermal growth factor receptor (EGFR), which may be overexpressed in tumour cells. Here, genomic testing was not used to pre-select patients for the clinical trials. Retrospective analyses of pharmacogenomic data on EGFR expression showed differences in response.

The SPC states that "in the 45 % of patients with known EGFR-expression status, the hazard ratio for survival was 0.68 (CI 0.49-0.94) for patients with EGFR-positive tumours and 0.93 (CI 0.63-1.36) for patients with EGFR-negative tumours". These results were obtained by retrospective sub-group analysis and could not be used to exclude EGFR negative patients from the indication. However, the indication contains a statement that "no survival benefit or other clinically relevant effects of the treatment have been demonstrated in patients with EGFR- negative tumours".

Considering that clinical efficacy was shown for the whole population the product was approved for the whole target population.

It has been estimated that 2200 patients instead of 470 patients would have been needed to show clinical benefit for Herceptin®, if patients had not been pre-selected based on genetic tests .[30] Apart from the increased development costs, a large number of patients would receive the product without benefiting (but with the associated adverse reactions). At least in oncology, it seems unethical not to use pharmacogenomics, if evidence of involvement of genetic factors exists.

The 2 examples of targeted cancer therapy illustrate the dilemma with including pharmaco-genomics in drug development. Using genomic markers in the analysis of the primary endpoint or to pre-select patients for a study is likely to restrict the indication and, hence, the market potential. For less severe diseases this may be a major disincentive for using pharmacogenomics. However, excluding potential non-responders will increase the risk

benefit ratio for the product. In some cases, only a restriction to the likely responders will make the product viable.

The pathophysiological basis of cancer is that cells have acquired genetic defects. It seems an obvious target in drug development to exploit the genetic differences between cancer and normal cells and to include pharmacogenomics in clinical development. For other diseases, genetic aspects may not be apparent or may be very complex (multi-gene involvement). Nevertheless, as knowledge expands, it can be expected that pharmaco-genomics will become part of primary analysis in other disease areas. For example, a recent EMEA *Reflection Paper on the Use of Genomics in Cardiovascular Clinical Trials* recommends dedicated trials with appropriate power calculations (see Section 7.3).[31]

Depending on the mechanism of action, the type of disease and the intended indication it should be decided whether to exclude certain genotypes from clinical trials (e.g. Herceptin®) or whether to stratify or enrich populations by their genomic traits for confirmatory analyses of different genotypes (e.g. future cardiovascular trials). The latter approach may or may not result in a genomically restricted indication.

6.2.2 Exploratory Endpoints

For the foreseeable future there will be very few genomic biomarkers that are suitable to be used in confirmatory analyses. However, for many diseases there are a number of putative genomic biomarkers that may be studied during drug development. The level of validity of these is variable and may range from probably valid to speculative. The biomarkers may relate to primary pharmacodynamics (identification of responders/non-responders) or may relate to secondary pharmacodynamics (identification of patients at risk of adverse reactions). In addition to studying putative genomic biomarkers, there is also the option to search for new genomic biomarkers during the clinical development, for example, by using whole genome sequencing. In any case, drug developers have to decide if and when to incorporate pharmacogenomics into their clinical trials.

When developing products for diseases where there is some evidence of the involvement of genetic factors in either the disease pathophysiology or in pharmacodynamics of drugs, pharmacogenomics should be included in clinical trials. This situation would arise when certain target genes are known or have been postulated, and tests have been described. In these cases collecting pharmacogenomic data as secondary endpoints should be considered.

Using genomic biomarkers as secondary endpoints in clinical trials is unlikely to have a direct impact on the product label. In most cases the pharmacodynamics of drug action involves several genes, each showing polymorphisms. Compared to the other extrinsic and intrinsic factors affecting drug action, the genetic variability may be insignificant. However, it may be possible to describe risk factors and warnings for both, desired and undesired actions. For severe diseases, where mistreatment can have harmful consequences

and for situations, where severe adverse reactions are observed, genomic testing prior to treatment may be justified, even if the utility has not been demonstrated conclusively.

The potential merits of collecting data on putative genomic biomarkers during development will be discussed using Ziagen® (abacavir)[32] as an example. Ziagen® is used in antiviral combination therapy for the treatment of Human Immunodeficient Virus (HIV) infection. In clinical trials approximately 5% of subjects receiving abacavir developed hyper-sensitivity reactions (HSR), which were life threatening or fatal in some cases.

The initial SPC in 1999 stated that "risk factors which could predict the occurrence or severity of abacavir HSR have not been identified" (*Scientific Discussion,* 2000). Subsequently, in retrospective case control studies, genetic polymorphisms in HIV infected subjects who developed HSR were compared with those who did not. The studies showed that "the HLA-B5701 gene may be a useful biomarker in Caucasian males and females. However, HLA-B5701 is not predictive of the risk of HSR in all other ethnic groups and both genders" (*Scientific Discussion,* 2005).

The current SPC concludes that "carriage of HLA-B*5701 is associated with a significantly increased risk of clinically suspected hypersensitivity in Caucasians." While there is a strong association between HLA-B5701 polymorphism and HSR (50% of patients with HLA-B*5701 develop HSR, 3% of patients without HLA-B*5701) there is also a large number of HSRs (50%) in Caucasian patients without the polymorphism. Therefore, the SPC does not recommend genotyping as a basis for clinical decision making. However, a recent paper describes that prospective testing in an ethnically mixed French HIV population has resulted in a reduction of HSR, from 12% (before screening) to 0%.[33] The example of Ziagen® shows that pharmacogenomics may be used to significantly reduce the occurrence of adverse reactions without severely restricting the target patient population.

During clinical trials a whole range of phenotype parameters (sex, body weight, ethnicity) are collected and analysed. The data are routinely used to analyse efficacy and safety in phenotypically defined subgroups. If clinically relevant, the results may be mentioned in the SPC. An example, where ethnicity has been shown to influence efficacy, is Iressa® (gefitinib), for which survival benefit has been observed in Asians only.[34] In 2005, FDA approved BiDil® (isosorbide dinitrate and hydralazine hydrochloride) for "the treatment of heart failure in self-confessed black patients", after efficacy in the whole population had not been demonstrated.[35, 36] It can be assumed that skin colour or "self-confessed ethnicity" are just surrogates for some underlying genetic variants which are more common in one ethnicity than in others. Stronger associations may be found, if genotype parameters are analysed instead of phenotype parameters. There may be instances where the collection of pharmacogenomic data may salvage a development programme, if only a subgroup (but not the whole study population) shows positive benefit risk ratio.

In this context it is worth noting that both the EU and the US regulations require the identification of subgroups with different safety and efficacy profiles. The *EU Directive*

2001/83/EC [37] states that "any patients or patient groups at increased risk shall be identified and particular attention paid to potentially vulnerable patients who may be present in small numbers, e.g., children, pregnant women, frail elderly, people with marked abnormalities of metabolism or excretion etc." The *US Code of Federal Regulations*[38] state that "if evidence is available to support the safety and effectiveness of the drug only in selected subgroups of the larger population with the disease, the labelling shall describe the evidence and identify specific tests needed for selection or monitoring of patients who need the drug".

There are obvious benefits from including genomic biomarkers in clinical development. Ideally, all patients in all studies would be tested. To limit the amount of testing, other strategies may be used. For example, all patients withdrawn due to failure of efficacy and/or all patients withdrawn due to adverse events may be tested (preferably including matched controls).

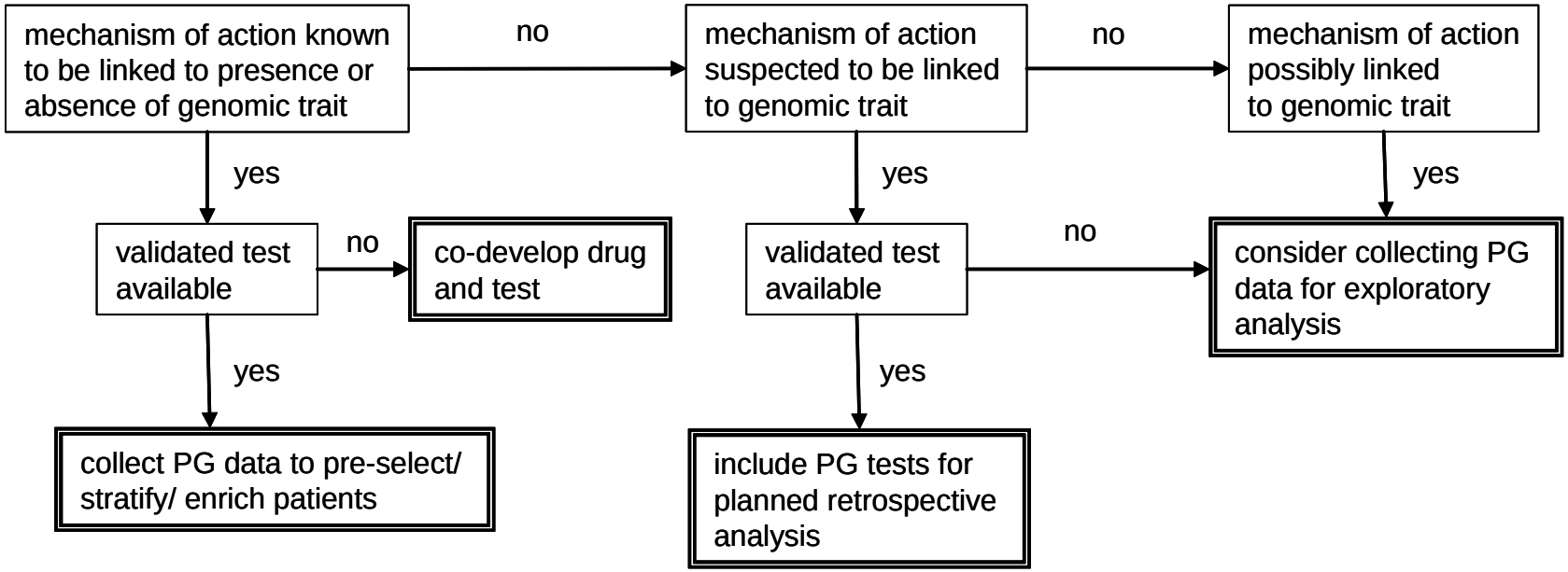
Collecting exploratory pharmacogenomic data (such as gene expression profiling, whole genome sequencing) during clinical trials may be useful to build a genomic data base in an otherwise well characterised patient population. New associations between gene and drug effect may be identified, and new hypotheses on the genetic involvement may be generated. There are a number of examples where important genomic biomarkers were discovered after the product had been approved. Collecting exploratory pharmacogenomic data during development will help to identify these biomarkers earlier.

Exploratory pharmacogenomic data collection (such as whole genome sequencing) may produce vast amounts of data that are prone to chance associations. The reliability of the data may be variable, and reproducibility may be an issue. However, more focussed approaches, such as sequencing of all genes related to immune response, may become available. In any case, exploratory pharmacogenomic data are not intended for regulatory decision making, and approval of the drug should not be affected. If the data indicate medically important associations, these should be verified in later studies or after approval. However, with the accelerating speed of progress in this area, it can be assumed that genomic data collected during clinical development will become more and more valuable.

Collecting genomic data may allow further retrospective analyses at some later time point, if new hypotheses are suggested. It may also be possible to carry out further tests on stored biological samples, if new biomarkers are proposed. However, if further tests are planned, consent has to be considered. In this context it is worth mentioning that EMEA is preparing guidance on *Pharmacogenomic Samples, Testing and Data Handling*[39] and on *Biobanks Issues Relevant to Pharmacogenetics*,[40] which will cover both technical and ethical aspects.

In conclusion, decisions on using pharmacodynamics related genomic biomarkers during clinical trials should be based on a number of factors. The main criteria, depicted in the proposed decision tree (Figure 3), are the level of knowledge on genetic involvement in drug action and the availability and validity of genomic tests . These may lead to using genomic tests to preselect, stratify or enrich patients in confirmatory studies. Alternatively, genomic biomarkers may be used for planned retrospective analyses or for purely exploratory analyses.

Figure 3 Pharmacodynamics Related Pharmacogenomic Data Collection in Phase 2/3 Safety and Efficacy Studies.



7 Regulatory Initiatives to Promote the Use of Pharmacogenomics

Pharmacogenomics is a new field in drug development. As yet it is not clear how it will impact on established drug development models. Regulatory bodies have started developing guidance in this area, but at this point most of the available guidance is still draft or at a concept phase.

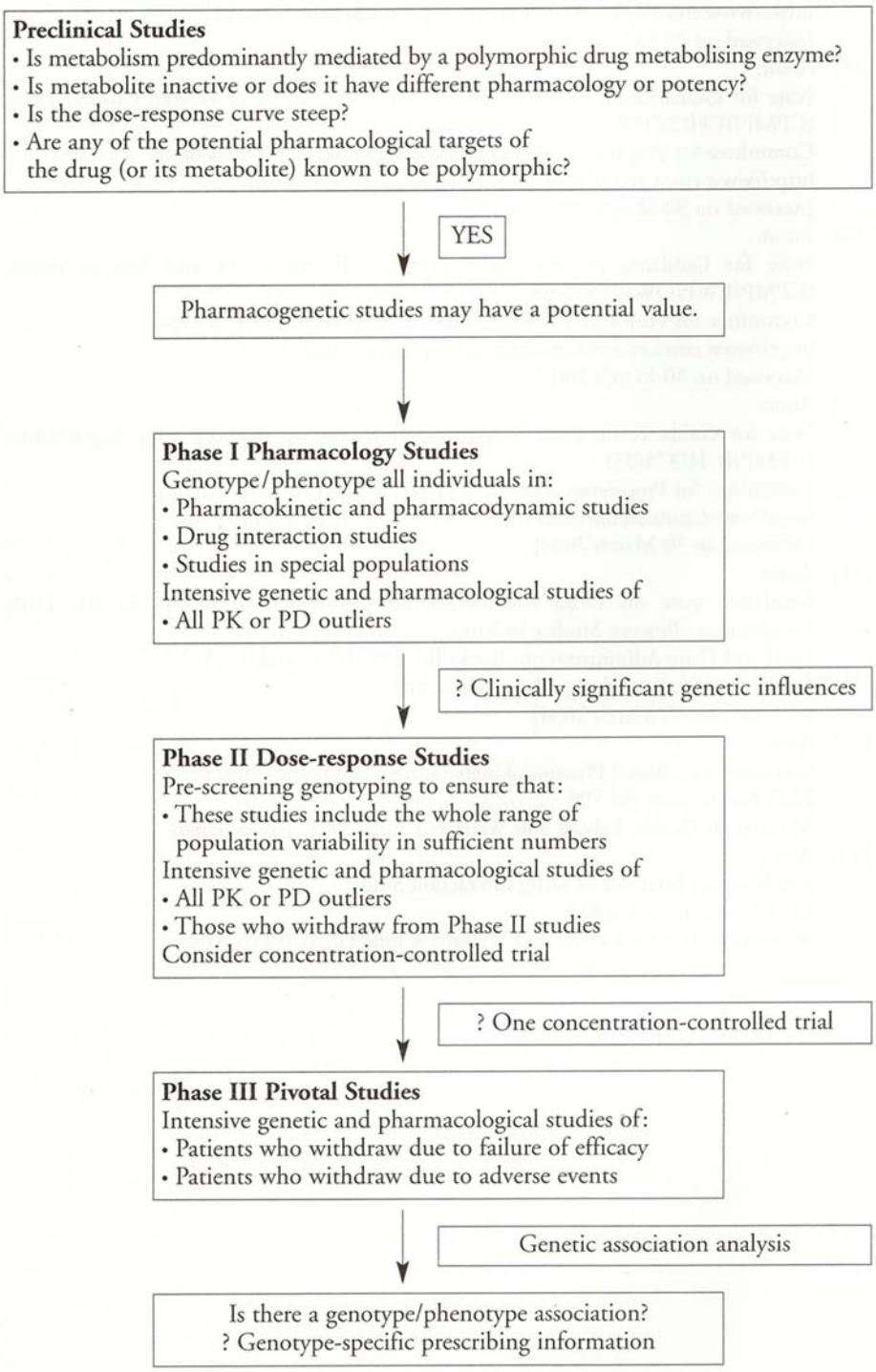
7.1 CIOMS

The Council for International Organisations of Medicinal Sciences (CIOMS) is an international, non-governmental, non-profit organisation, established jointly by WHO and UNESCO. The membership of CIOMS includes 48 international member organisations, representing many of the bio- medical disciplines and 18 national members, mainly representing national academies of science and medical research councils. CIOMS is representative of a substantial proportion of the biomedical scientific community. Regulatory agencies are not members, but participate indirectly, and agency staff contribute to CIOMS publications. Therefore CIOMS represents current scientific and regulatory thinking. Publications by CIOMS have no direct regulatory impact, but they set norms that are likely to become accepted standards.

Between February 2002 and April 2004 the CIOMS Working Group on Pharmacogenetics met 5 times. As a result the book *Pharmacogenetics – Towards Improving Treatment with Medicines* was published in January 2005.[7] The book covers various aspects of pharmacogenomics, including the use in drug development.

When deciding whether to include pharmacogenetics to study pharmacokinetic effects in clinical development, the CIOMS approach depicted in the following diagram may be useful (Figure 4). Pharmacogenetic studies should be considered for all stages of clinical development. Where preclinical evaluation suggests genetic involvement, it is recommended to genotype and/or phenotype all subjects in most of the Phase 1 studies. In addition, intensive genetic and pharmacological studies of all pharmacokinetic or pharmacodynamic outliers are recommended. Rather than genotyping all subjects in Phase 2 and 3 studies, it is suggested to concentrate genetic testing on outliers. This may include all pharmacokinetic and pharmacodynamic outliers in Phase 2 studies. In Phase 3 studies all patients who withdraw due to failure of efficacy and due to adverse events may be tested. For Phase 2 studies it is also suggested to pre-screen subjects to ensure that the studies include the whole range of population variability in sufficient numbers. Another concept to be considered for Phase 3 are concentration controlled trials.

Figure 4 Integrating pharmacogenetics in drug discovery and development (CIOMS, 2005[7])



7.2 FDA

Over the last few years FDA has taken considerable effort to develop guidance on pharmacogenomics. Following a workshop, co-sponsored with pharmaceutical industry groups in 2002, and a presentation to FDA science board in April 2003, FDA published a draft version of the Guidance for Industry on *Pharmacogenomic Data Submissions*. The guideline was finalised in March 2005.[9] In parallel with this guideline, manuals of policies and procedures (MAPPs) were finalised, outlining the organisation, principles and function of the inter-centre Interdisciplinary Pharmacogenomics Review Group (IPRG) and explaining how voluntary genomic data submissions will be received and reviewed at the agency.[41, 42, 43]

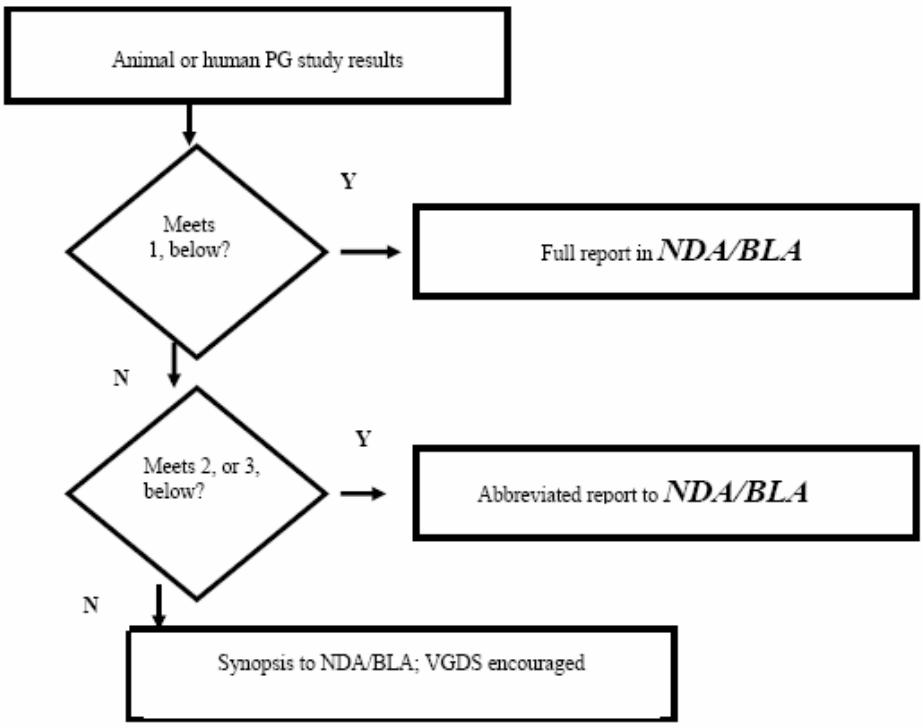
It is FDA's stated intention to guide development of PG to "benefit both drug development programmes and public health". As outlined "the FDA developed this guidance to facilitate the use of PG test during drug development and encourage open and public sharing of data and information on pharmacogenomic test results".

According to the US *Code of Federal Regulations*,[44] sponsors have to submit data relevant to drug safety and effectiveness during development (IND) or as part of drug applications (NDA, BLA). In practice this leads sponsors to submitting all data. At this point most of the pharmacogenomic data are exploratory, and the relevance to drug safety and effectiveness is unknown. In the guidance FDA states that "because these regulations were developed before the advent of widespread animal or human genetic or gene expression testing, they do not specifically address when such data must be submitted". The guidance intends to clarify what data submissions are mandatory. For a sponsor, considering the inclusion of exploratory pharmacogenomics in a clinical development programme, it is important to gain a clear understanding of what data do not need to be submitted.

The guidance provides several decision trees on the requirements for and the format of genomic data submissions. The decision trees cover submissions of pharmacogenomic data to INDs, to new NDAs, BLAs or Supplements and to approved NDAs, BLAs or Supplements. As an example, the decision tree for submissions of pharmacogenomic data to new NDAs, BLAs and Supplements is shown below (Figure 5). In the context of NDAs, genomic data submissions are mandatory if the sponsor uses the results to support scientific arguments about dosing, safety, patient selection or effectiveness. They are also mandatory if the sponsor proposes to describe the results in the drug label, or if tests are essential to achieving the dosing, safety or effectiveness described in the drug label. In these circumstances a full report will be required. If the sponsor is not relying on or mentioning the information in the drug label, and if the test results represent probable valid biomarkers, abbreviated reports will be required. Synopses are required for information on exploratory or research studies which do not use known valid or probably valid biomarkers.

The guideline also provides several detailed examples for mandatory or voluntary submissions. More detailed discussions on selected case studies from a 2003 workshop, co-sponsored by FDA, have also been published.[45]

Figure 5 Submission of Pharmacogenomic (PG) Data to a New NDA, BLA, or Supplement (FDA, 2005[9])



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1. The sponsor will use the test results in the drug label or as part of the scientific database being used to support approval as complete submissions (not in the form of an abbreviated report, synopsis, or VGDS), including information about test procedures and complete data, in the relevant sections of the NDA or BLA. If the pharmacogenomic test is already approved by the FDA or is the subject of an application filed with the Agency, information on the test itself can be provided by cross reference.

   The following examples would fit this category.

   – Pharmacogenomic test results that are being used to support scientific arguments made by the sponsor about drug dosing, safety, patient selection, or effectiveness

   – Pharmacogenomic test results that the sponsor proposes to describe in the drug label

   – Pharmacogenomic tests that are essential to achieving the dosing, safety, or effectiveness described in the drug label

2. The test results are known valid biomarkers for physiologic, pathophysiologic, pharmacologic, toxicologic, or clinical states or outcomes in the relevant species, but the sponsor is not relying on or mentioning this in the label. Submit to the Agency as an abbreviated report (not as a synopsis or VGDS). If a pharmacogenomic test of this type was conducted as part of a larger overall study, the reporting of the pharmacogenomic test results can be incorporated into the larger study report.

3. The test results represent probable valid biomarkers for physiologic, pathophysiologic, pharmacologic, toxicologic, or clinical states or outcomes in the relevant species. Submit to the Agency as an abbreviated report. If the pharmacogenomic testing of this type was conducted as part of a larger study, the abbreviated report can be appended to the report of the overall study.

4. Information from general exploratory or research studies, such as broad gene expression screening, collection of sera or tissue samples, or results of pharmacogenomic tests that are not known or probable valid biomarkers to the NDA or BLA are not required to be submitted. Because the Agency does not view these studies as germane in determining the safety or effectiveness of a drug, the submission requirements in §§ 314.50 or 601.2 will be satisfied by the submission of a synopsis of the study. However, the Agency encourages the voluntary submission of the data from the study in a VGDS submitted to the NDA or BLA.

For data that do not fall into the mandatory data submission category, FDA encourages voluntary genomic data submissions (VGDSs). The purpose of VGDS is two fold. The FDA hopes to gain better understanding of the scientific issues and to become more familiar with genomic submissions. Eventually this will find its way into policy development. For the sponsor the potential benefits include meeting informally with FDA to receive assessments of scientific data from pharmacogenomic experts. This will allow to obtain insight into the evolving regulatory decision making process.

The key concept of VGDSs is that FDA will not use these data for regulatory decision making. In the context of this guideline, regulatory decision making is defined as any decision by FDA in the evaluation of pharmacogenomic information used to establish dosing, safety or effectiveness of a drug.

To ensure that VGDSs are kept separate from data submitted in the context of INDs, NDAs and Supplements, FDA has established procedures for receipt, processing and reviewing of VGDSs.[42] Most importantly, the members of IPRG are different and independent from the FDA staff who will review drug applications.[41]

The VGDSs are completely separate from data submissions to drug applications. Consequently, should additional data validate a biomarker after data have been submitted voluntarily, the sponsor must re-submit the data to the appropriate application.

A further FDA initiative is the April 2005 *Drug-Diagnostic Co-Development Concept Paper*,[27] which addresses issues related to the development of *in vitro* diagnostics for mandatory use in decision making about drug selection. The concept paper reflects FDA "thoughts on how to prospectively co-develop a drug or biological therapy (*drugs*) and a device test in a scientifically robust and efficient way". Such co-development is encouraged whenever tests are recommended in the product label. However, the co-development may become necessary, if a sponsor decides to develop a drug solely in populations from which certain patients were excluded based on pharmacogenomic testing. Elsewhere, FDA states that they "would be unable to approve a drug for which the risk or benefit was predicated on a pharmacogenomic test that was unavailable to prescribers".[9] Therefore the test has to be commercially available or has to be provided by the company marketing the medicinal product.

The scope of the concept paper[27] includes tests for the selection of patients who are likely or unlikely to respond and those who are likely to exhibit adverse events. The paper does not specially cover issues related to pharmacogenomic testing for the purpose of drug dosing determination (e.g. tests for metabolic enzymes).

The concept paper addresses review procedure issues, such as classification as combination product, intercenter review and formal industry FDA interactions (IND and IDE meetings).

Further, it covers issues related to clinical test validation and the demonstration of clinical test utility. Consequently, there is some focus on clinical trial design and its statistical principles. Possible label implications of the different trial designs are also discussed. It is intended to supplement the *Drug-Diagnostic Co-Development* guideline with a guideline on *Pharmacogenetic Tests and Genetic Tests for Heritable Markers*, which is currently available as draft (Feb 2006).[11] A further concept paper, *Recommendations for the Generation and Submission of Genomic Data*, published in November 2006, deals with technical aspects related to pharmacogenomic tests.[46]

The FDA website hosts a section on pharmacogenomics[47] providing links to the relevant guidelines, publications by FDA staff and external links. Resources include a *Table of Valid Genomic Biomarkers in the Context of Drug Labels*[14] and *Tables of Substrates, Inhibitors and Inducers* relevant for the study of drug drug interaction.[24]

7.3 EMEA

EMEA launched its activities on pharmacogenomics in June 2000 with a seminar on pharmacogenetics, attended by experts from CPMP, industry and patient organisations. In April 2001, CPMP established a working group on pharmacogenetics (PGWP). The working party is multidisciplinary in composition. It includes independent experts in medicines evaluation as well as experts in diverse scientific, ethical and regulatory matters relevant to the new genomic technologies. According to the mandate published in 2005,[48] PGWP will "provide recommendations to CHMP on all matters relating directly or indirectly to pharmacogenetics". In particular, the activities include: conduct of PG workshops and briefing meetings, preparation and review of guidelines, assessment of the pharmacogenomic parts of regulatory submissions, support dossier evaluation to ensure consistency across applications and contribution to scientific advice.

In December 2001, PGWP released a *Position Paper on Terminology in Pharmacogenetics* for consultation (see section 4). This paper has been finalised and came into operation in June 2003.[8] The guideline on *Pharmacogenetics Briefing Meetings* was finalised in April 2006[49] and will be discussed below.

The guideline introduces the concept of informal pharmacogenetic briefing meetings. The stated objectives of the briefing meetings are to "allow applicants and PGWP to share and discuss in an informal setting the technical, scientific and regulatory issues that arise by the inclusion of pharmacogenetics and pharmacogenomics in the development strategy and to assess their potential implications in the regulatory processes". The meetings are intended to contribute to minimising any obstacles that may prevent the use of pharmacogenomic technology in drug development. In addition, PGWP wishes to learn about circumstances and rationales under which pharmacogenomic data is generated. This will enable the group

to provide reflection on the issues discussed at briefing meetings to CHMP and to other CHMP working groups.

The applicant has the opportunity to gain input on pharmacogenomic aspects of development plans from PGWP in an informal setting. The data and issues discussed will not have any regulatory impact. In addition, the document gives guidance on the format of pharmacogenomic submissions for informal regulatory meetings.

The general concept of the pharmacogenomic briefing meetings is similar to the FDA VGDSs. However, EMEA views the briefing meetings as an additional opportunity for applicants to discuss their development strategy. For example, there is no emphasis on the separation of data submitted as part of the briefing meetings and other submission. Instead, it is "strongly recommended that the applicant includes the summary of the briefing meetings in any subsequent dossier".

According to *EU Directive 2001/81 as amended* "all information, which is relevant to the evaluation of the medicinal product concerned, shall be included in the application, whether favourable or unfavourable to the product".[50] The guidance on pharmacogenetics briefing meetings does not define what may be considered relevant in the context of exploratory genomic data. Compared to the US guidance, this may leave some uncertainty to what extend exploratory data need to be reported and how they will be reviewed. Pharmacogenomic tests, such as whole genome sequencing, may produce vast amounts of data, and for applicants it is important to define what detail needs to be reported and in which format.

The scope of the briefing meetings is kept broad and may include exploratory and valid biomarkers. This allows sponsors to discuss any aspect of pharmacogenomics.

As another initiative in pharmacogenomics, EMEA plans to develop guidance for specific diseases to focus on pharmacogenomic aspect of pharmacodynamic targets. A first reflection paper in this area covers the use of genomics in cardiovascular clinical trials.[31] In this paper the current status of pharmacogenomics is reviewed and its limitations are recognised. However, EMEA advocates the inclusion of pharmacogenomics in cardiovascular trials. The recommendations may be summarised as follows:

> The power in pharmacogenomic studies should be adequately addressed. Useful information may be obtained by studying associations of genomic variations with treatment efficacy in large ongoing trials. However, dedicated trials with appropriate design and power calculation are "strongly warranted".
>
> Results should be replicated either in a second trial with a similar design and endpoints or in an enriched design.
>
> The mechanism of action involved in the genomic differences should be investigated.

EMEA states that these are general recommendations which "may be applicable to pharmacogenomic association studies for other common complex diseases".

Apart from the scientific and regulatory aspects, ethical aspects have to be considered during clinical development. Ethical aspects may significantly increase the complexity of a planned study and may even jeopardize its feasibility. To address technical and ethical issues, EMEA is currently developing 2 guidance documents, namely, *Pharmacogenomic Samples, Testing, and Data Handling*[39] and *Biobanks Issues Relevant to Pharmacogenetics*.[40] Consent by study subject may also be an issue in pharmacogenomic studies. To this end, EMEA has published the paper *Understanding the Terminology used in Pharmacogenetics* directed at patients and study participants.[51]

7.4 Joint FDA EMEA Initiatives

In May 2006, FDA and EMEA issued *Guiding Principles on Processing Joint FDA EMEA Voluntary Genomic Data Submissions (VGDSs) within the Framework of the Confidentiality Agreement*.[52] The document explains how requests for joint FDA-EMEA VGDS briefing meetings are received, processed and reviewed by the agencies. For the sponsor it is optional to request a joint FDA-EMEA briefing meeting.

In this paper, the 2 agencies confirm that they pursue the same strategy in pharmacogenomics, namely to encourage voluntary genomic data submissions. The VGDSs are "used to help the agencies to gain an understanding of genomic data, and are not part of regulatory decision making processes".

The outlined process is essentially the same as the processes used for other VGDSs and pharmacogenetics briefing meetings at the respective agencies. The paper specifies a clear separation between the VGDS process and the dossier review procedures and teams at both agencies. For the FDA this is according to their guideline on VGDSs. However, for EMEA the mentioned separation is more specific than in the respective guideline.

At this point no reports on any joint VGDS meetings have been published.

8 Conclusions

Polymorphisms of a number of drug metabolising enzymes have been well characterised and are considered valid biomarkers. Where these enzymes are predominately involved in the metabolism of the drug, the inclusion of pharmacogenomics in pharmacokinetic studies is recommended by the relevant guidelines. Testing for these polymorphisms in healthy volunteers has become standard and commercial tests are available. Pharmacogenomic testing of drug metabolising enzymes is sometimes extended to patient studies, if a relationships between polymorphisms and pharmacodynamic action has to be assessed. It can be expected that the number of valid markers relevant to pharmacokinetics (metabolising and other enzymes, transporters) will continue to increase. As a consequence the number of drug labels containing genetic information in the dosing, warnings and drug interaction sections will continue to increase. Whether there will be many drugs with mandated pharmacogenomic tests for prescription remains to be seen. One reason why this may not happen is that drugs, which are subject to significant genetic variability, are more likely to be dropped during early development.

As yet, there are only a few valid genomic biomarkers for pharmacodynamic action. In targeted cancer therapy they have been used for patient selection, and the respective genomic tests have to be used before prescription of the drugs. The availability of valid genomic biomarkers for other diseases and pharmacological targets is likely to increase.

There are many examples where important genomic factors were discovered after the drug had been on the market for some time. These drugs may have been developed decades ago, when pharmacogenomics either did not exist or was not considered during drug development. Today, pharmacogenomics has evolved to such an extent that it should be considered at every stage of development. However, most of the pharmacogenomic tests are still exploratory, and it is up to the pharmaceutical companies to include these in their clinical development programmes.

The potential advantages of integrating pharmacogenomics in the clinical development of drugs include: better defined doses, better defined target patient population (exclusion of poor responders), exclusion of patients likely to develop adverse drug reaction. These advantages may give a new drug a competitive advantage and may allow higher reimbursement to be achieved.

On the other hand, there are potential disadvantages connected with pharmacogenomics: restricted target patient populations, higher development costs, mandatory or recommended tests before prescription. These aspects may adversely affect the market potential of a new drug. It is worth noting though that the pathophysiology of most diseases and the mechanisms of pharmacokinetic and pharmacodynamic action are polygenetic. In most instances a genotype or particular gene expression profile is likely to be one of a number of risk factors (for adverse reactions or favourable response). Therefore, pharmacogenomic

biomarkers might be collected like other, non-genomic predictive markers (e.g. blood pressure, level of liver enzymes).

The uptake of pharmacogenomics may be slow, but it is likely to become an integral part of drug development. One obstacle has been the uncertainty how genomic data will be used by regulatory authorities during the approval process. Exploratory genomic data cannot be used to demonstrate efficacy, and no label claims may be obtained. However, for safety issues the level of evidence required is lower, and exploratory data could be considered sufficient for regulatory decision making. The recent guidance by FDA and EMEA addresses these concerns and encourages the inclusion of pharmacogenomics in drug development.

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Hiermit erkläre ich von Eides statt, die Arbeit selbstständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben