usually genotyped but available evidence suggests that a substantial proportion of the cases of the drug-induced long QT syndrome might represent cases of "*forme fruste*" of the congenital long QT syndrome.

Understanding genetic variation in pharmacological targets during drug discovery allows preclinical evaluation of any alterations in the affinity of an NCE for these targets and the clinical response to the NCE that can then be explored and evaluated clinically. This data might be of interest for appropriate patient selection, safety monitoring, or any other factor affecting the future performance of the NCE. For example, NCEs are now routinely evaluated for their affinity to bind to the hERG channel, as this most likely predicts the clinical potential for QT interval prolongation. It is clear, however, that a full functional characterisation of any newly discovered polymorphism in a pharmacological target is required before its full significance for the future development of an NCE can be assessed. Unless the full functional consequences are known, it may be impossible to correlate a genotype with drug response. However, it would be inappropriate to require that full functional significance of a polymorphism be known for a marker to have a utility in guiding drug development and delivery. It is not possible at present to say that we have full knowledge of the drug targets of biomarkers such as lipid levels although their utility in improving healthcare is accepted.

It appears that polymorphisms of pharmacological targets may prove to be more relevant clinically than the polymorphisms of drug metabolising enzymes. In a pharmacogenetic study that compared paroxetine and mirtazapine in 246 elderly patients with major depression, discontinuations due to paroxetine-induced side effects were strongly associated with the 5-HTR_{2A} C/C, rather than CYP2D6, genotype. There was a significant linear relationship between the number of C alleles and the probability of discontinuation. The severity of side effects in paroxetine-treated patients with the C/C genotype was also greater [34]. Thus, although paroxetine is metabolised by CYP2D6, polymorphism of 5-HTR_{2A} is a more important determinant of paroxetine-induced ADRs.

3. Pharmacogenetics: Drug development, approval and restrictions

3.1 Termination of drugs from development

Until the completion of the Human Genome Project and the availability of technology to scan the entire genome for SNPs that correlate with

genetically determined drug response, there was (and there still appears to be) a general reluctance within the industry to continue the development of drugs subject to significant genetic variability. For example, predominantly CYP2D6-mediated metabolism of a potential NCE has frequently been seen as a liability ('2D6-liability') and a number of such compounds in 1980s and early 1990s were dropped from further progression. Efforts were instead directed at developing structural analogues of lead compounds that were not eliminated predominantly by CYP2D6-mediated metabolism. A similar situation seems to have now arisen with respect to NCEs that block hERG channels, conferring a 'QTc liability' to the NCE.

Terikalant, a class III antiarrhythmic drug, is metabolised by CYP2D6. It has been shown that the increase in QT interval produced by terikalant correlates well with the degree of impairment in its metabolic elimination by CYP2D6 [14]. The perceived difficulties in managing this genetically driven risk resulted in termination of this compound from further development. There is of course no readily available information on how many other compounds have been dropped during development due to their CYP2D6-mediated metabolism. This approach of discarding polymorphically metabolised candidate drugs has proven resource-intensive and counter-productive, leading to greatly diminished pipeline of innovative NCEs. The application of pharmacogenetics may therefore allow development decisions to be made that will facilitate the progression of NCEs. More recently, metabolism by CYP3A4 is also perceived to be a liability since these drugs (e.g. a number of QT-prolonging drugs or HMG-CoA reductase inhibitors) are highly susceptible to drug interactions.

More recently, the trend seems to be one of developing single isomers of previously marketed racemic drugs in cases where one of the isomers is subject to polymorphic metabolism and introduces wide interindividual variability in AUC at a given dose. This variability can be reduced, with a more predictable efficacy, by eliminating one isomer and administering only the isomer, which is efficacious but less subject to polymorphic metabolism. For example, in case of omeprazole, the ratios of AUC for PMs/EMs of CYP2C19 are 7.5 for (+)-(R)-omeprazole and 3.1 for (-)-(S)-omeprazole [35]. (-)-(S)-omeprazole is now approved and marketed as esomeprazole ('Nexium'). Whether or not this reduction in variability has any clinically relevant practical implications remains to be shown and each drug must be judged on a case-by-case basis. The message here is that drug development programmes should address pharmacogenetics in the context of stereoselectivity in the pharmacology of the NCE when appropriate.

3.2 Pharmacogenetically driven labelling restrictions

In order to comply with various regulatory recommendations, sponsors of NCEs often conduct formal phase I studies in a genotyped panel of healthy volunteers to characterise pharmacogenetic influences on pharmacokinetics. Unfortunately, however, the findings of such studies are rarely carried forward to improving the designs and inclusion criteria of phase II or phase III studies. It is most unusual to see phase II dose-ranging studies that include information on the genotype of the individuals randomised. This omission has serious implications for selecting the most appropriate dose for a pharmacogenetically heterogeneous population in phase III pivotal studies. Ideally, where drugs are metabolised by known polymorphic enzymes, phase II dose-ranging studies should include a wide range of prospectively pre-screened subjects to ensure the inclusion of all the important genotypic subgroups, thus impacting on the efficiency of drug development. It is encouraging to note that there is now a greater trend towards integrating pharmacogenetics in drug development.

In some cases where serious toxicity might have a pharmacogenetic basis, the management of clinical safety of an NCE requires detailed labelling on influences of pharmacogenetic factors. Five drugs best illustrate the current regulatory practice of incorporating candidate gene-based pharmacogenetic information into labels to promote safe and effective prescribing.

Thioridazine is metabolised by CYP2D6 and poor metabolisers of CYP2D6 have high plasma levels of the parent drug. Thioridazine predisposes individuals to excessive QT interval prolongation and torsade de pointes. Therefore, the US Food and Drug Administration (FDA) have now contraindicated the drug in patients known to have reduced levels of cytochrome CYP2D6.

Sertindole, an atypical neuroleptic agent, is primarily cleared by CYP2D6. The PMs utilise an alternative pathway mediated by CYP3A4 for its elimination. Since it is not a routine practice to genotype patients, PMs might be at risk if CYP3A4-mediated pathway was inhibited. Consequently, coadministration of sertindole is contraindicated with ketoconazole and itraconazole, both powerful inhibitors of CYP3A4.

S-citalopram (a potent selective serotonin re-uptake inhibitor) has been approved as 'escitalopram' for depression. It is metabolised predominantly by CYP2C19. The usual dosage is 10 mg once daily, which may be increased to a maximum of 20 mg daily. However, for patients who are known to be poor metabolisers with respect to CYP2C19, the recommendation is to initiate treatment with a dose of 5 mg daily during the first two weeks of treatment. Depending on individual patient response, the dose may be increased to 10 mg daily.

Celecoxib is an orally active, COX-2 selective inhibitor indicated for the symptomatic relief in treatment of osteoarthritis or rheumatoid arthritis. Since celecoxib is predominantly metabolised by CYP2C9, caution is advised when treating patients known to be CYP2C9 poor metabolisers. Fluconazole inhibits CYP2C9 and increases celecoxib mean Cmax by 60% and AUC by 130%. It is therefore recommended that celecoxib be used at half the normal doses in patients receiving fluconazole. Arising from the observed inter-ethnic differences in the pharmacokinetics of the drug, it is also recommended that in black patients, the lower dose (200 mg per day) should be used initially. The dose may, if needed, later be increased to 400 mg per day.

When additional data are or become available, a number of other sections of the prescribing information (e.g. special warnings and precautions for use, drug interactions, ADRs) may need to address the pharmacogenetic profile of potential patients. A recently approved drug that well illustrates this complexity of prescribing information is atomoxetine. This drug, approved by the US FDA in December 2002, is indicated for attention deficit hyperactivity disorder and is metabolised primarily through CYP2D6.

CYP2D6 polymorphism has not only the safety but also efficacy implications. PMs are at risk of a lack of efficacy when the therapeutic effect of a drug is mediated principally by its CYP2D6-generated metabolite. Examples here include codeine and encainide. In particular, PMs exhibit a relative loss of analgesic effects following administration of codeine or tramadol as well as a loss of antiarrhythmic effects following administration of encainide. The therapeutic effects of these drugs are mediated primarily by their metabolites, namely morphine, (+)-M1 metabolite of tramadol and O-desmethyl-encainide (ODE) respectively. In contrast, UMs are at risk from rapidly accumulating metabolites and of poor efficacy when the parent drug mediates the therapeutic effect, for example following administration of normal doses of nortriptyline or perhexiline.

Following results of the Cardiac Arrhythmias Suppression Trial (CAST), the indications for class I antiarrhythmic drugs have been severely restrict-

ed. It is interesting to speculate in retrospect on whether the increased risk of mortality associated with flecainide, encainide or moricizine in CAST may be explained by polymorphic metabolism of these drugs or by mutations of ion channels. Likewise, one may question the role of potassium channel mutations in the observed increase in mortality associated with d-sotalol in the Survival With Oral d-Sotalol (SWORD) study.

If drug response is shown to correlate with a particular SNP(s) or SNPs pattern (haplotype), prescribing information in the future may have to include information on not only in terms of drug metabolising enzymes or pharmacological targets but also in terms of SNP(s) or haplotypes.

3.3 Pharmacogenetics and drug withdrawals

In some cases of serious toxicity, it may not be possible to manage the clinical risk even after careful labelling changes, and a decision has to be made on whether the drug can be allowed to remain on the market. Circumstances leading to the withdrawal of a drug from the market are complex but a conspiracy of genetic factors with other factors (probably the presence of co-morbidity or co-medications) is evident in many drug withdrawals or in termination of clinical development.

The withdrawals of perhexiline and phenformin in late 1980s are almost certainly related to genetically mediated toxicity. Both these drugs are metabolised almost exclusively by CYP2D6 and their clinical uses were associated with serious neuropathy and hepatotoxicity (perhexiline) or lactic acidosis (phenformin). Available evidence strongly incriminates CYP2D6 as a risk factor for both. A number of other older drugs have now been removed from the market. There is a body of evidence which, when viewed collectively, also supports the notion that genetic factors may have contributed substantially to their withdrawal from the market. These drugs include encainide (CYP2D6), terodiline and prenylamine (CYP2D6 and potassium channel mutations) and terfenadine, cisapride and levacetylmethadol (potassium channel mutations).

4. Regulatory framework

It is evident from the foregoing that it is vital to address the influence of pharmacogenetic factors at all stages from research & development (R&D) to post-marketing surveillance of the NCE. Through various guidance notes, regulatory authorities have long articulated their recommendations on the need to address genetic factors during drug development. Not surprisingly, therefore, evaluation of influences of pharmacogenetic factors is also critical during regulatory evaluation and post-marketing clinical use of the drug. The development of an NCE may need to be terminated pre-approval, its labelling highly restricted during approval, or its clinical use suspended post-approval if variability from pharmacogenetics cannot be managed.

Although the requirements to address these genetic factors are stated by different regulatory bodies in different terms, the net effect of the requirements is that new knowledge concerning pharmacogenetic variations in drug response will lead to increased requirements for pharmacogenetic documentation. At present, a number of guidelines from the European Union's Committee for Proprietary Medicinal Products (CPMP), US Food and Drug Administration (FDA) and/or International Conference on Harmonisation (ICH) make direct or indirect references to the need for addressing genetic factors when developing new chemical entities. The guidelines from the CPMP and ICH are shown in Table 4.

Table 4
Pharmacogenetics and CPMP and ICH Guidelines

	Genetic Factors in Pharmacokinetics
1.	Pharmacokinetic Studies in Man [36]
2.	Drug Interactions [37]
3.	ICH - Ethnic factors in the acceptability of foreign clinical data [38]
4.	Bioavailability and Bioequivalence [39]
5.	ICH - Dose-response information [40] *"...metabolic polymorphism..."*
	Genetic Factors in Pharmacodynamics
6.	ICH - Dose-response information [40] *"variability in pharmacodynamic response..."*

The CPMP guideline on "Pharmacokinetic Studies in Man" requires that metabolic studies should indicate whether the metabolism of a drug may be substantially modified in a case of genetic enzyme deficiency and whether, within the dose levels normally used, saturation of metabolism may occur, thereby resulting in non-linear kinetics.

The CPMP guideline on "Drug Interactions" emphasises that subjects participating in metabolic *in vivo* interaction studies should be appropriately

genotyped and/or phenotyped if any of the 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, in a PM when an alternative route of metabolism is inhibited or in a heterozygous EM with compromised metabolic capacity.

In April 1997, the US FDA issued a guidance entitled "Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies In Vitro" [41]. This states "*Identifying metabolic differences in patient groups based on genetic polymorphisms, or on other readily identifiable factors such as age, race, and gender, could help guide the design of dosimetry studies for such populations groups. This kind of information also will provide improved dosing recommendations in product labelling, facilitating the safe and effective use of a drug by allowing prescribers to anticipate necessary dose adjustments. Indeed, in some cases, understanding how to adjust dose to avoid toxicity may allow the marketing of a drug that would have an unacceptable level of toxicity were its toxicity unpredictable and unpreventable.*"

The Japanese Koseisho has also issued guidelines in 2001 that recommend genotyping in all drug development programmes for drugs that are metabolised by cytochrome P450s [42, 43].

The ICH guideline on 'Dose-Response Information to Support Drug Registration" recognises that the choice of a starting dose might also be affected by potential interindividual variability in pharmacodynamic response to a given blood concentration level, or by anticipated interindividual pharmacokinetic differences, such as could arise from metabolic polymorphisms or a high potential for pharmacokinetic drug-drug interactions.

It is also recognised by various regulatory guidelines that certain types of ADRs are due to unusual genetically determined pharmacokinetic variations and it is advised that every effort must be made to elucidate the pharmacokinetic mechanisms if there is any reason (e.g. from the knowledge of secondary pharmacology) to suspect that the ADR is caused by the altered pharmacokinetics of the drug.

One important question regarding the demography of a clinical trial population is the extent to which it represents the target population in terms of genetic, pharmacokinetic and pharmacodynamic variability.

Regulatory guidelines acknowledge the importance of inter-ethnic differences in pharmacokinetics and pharmacodynamics of drugs resulting from non-genetic extrinsic factors as well as from global heterogeneity in the frequency of variant alleles of drug metabolising enzymes or pharmacological targets. This global heterogeneity assumes considerable importance now that sponsors often conduct their studies in populations distant from the ultimate target populations. This global development reduces costs, expedites drug development and addresses the issues arising from global prescribing of drugs. The ICH guideline on "Ethnic Factors in the Acceptability of Foreign Clinical Data" recommends that a regulatory submission should include (1) adequate characterisation of pharmacokinetics, pharmacodynamics, dose-response, efficacy and safety in the population of one region and (2) characterisation of pharmacokinetics, pharmacodynamics and dose-response in the new region. The guideline recognises the role of genetic factors and the steepness of the dose-response curve in determining whether a drug is likely to show significant ethnic differences during its clinical use.

The CPMP guidance note on Investigation of Bioavailability and Bioequivalence also recommends that phenotyping and/or genotyping of subjects may be considered for safety or pharmacokinetic reasons.

The utilisation of genetic information in global development programmes, including bridging studies between populations, will be an area of increasing activity and regulatory interest.

5. Investigating pharmacogenetic influences during drug development

Although the emphasis of the following sections is exploration and characterisation of variability due to genetic factors and genetic influences on drug response, the role of non-genetic factors should not be overlooked during drug development.

5.1 Preclinical studies

During the preclinical phase, a wealth of *in vitro* and *ex vivo* data are generated, which provide direct and indirect indications of possible pharmacogenetic implications for the compound under investigation. The recommendations from the US FDA and the CPMP regarding the design and use of *in vitro* studies for drug-drug interactions make explicit references to pharmacogenetic polymorphisms of drug metabolising enzymes.

With the aid of current *in vitro* approaches, it is possible to tentatively identify very early during the drug discovery and development process the main metabolites and enzymes catalysing the principal metabolic routes of practically any NCE.

In vitro studies provide a direct indication of the participation, or lack thereof, of polymorphic enzymes in the metabolism of an NCE (see table 5), although unqualified extrapolation to clinical setting should not be assumed.

Preclinical data using liver microsomes of course have their own limitations since it is now known that many drug metabolising enzymes are also expressed in other tissues such as the gut wall and these play a substantial role in drug elimination.

The "go/no-go" decision can then be made, based on both qualitative and quantitative information on the role of polymorphic enzymes in the *in vitro* study of an NCE. If it is decided to continue the development of the NCE, these *in vitro* metabolic data provide a rational basis for planning appropriate pharmacological (pharmacogenetic) and clinical studies in a genotyped panel of healthy volunteers and/or patients (for example, with respect to CYP2D6 or CYP2C19) to assess their *in vivo* significance on the kinetics and the dynamics of the compound under study. Observations on the influence of pharmacogenetic factors on the pharmacokinetics of a drug have in the past led to termination of development, restricted labelling or withdrawal of the drug from the market. For these early pharmacogenetic data to be of practical value in terms of labelling and clinical use, it is necessary to show their clinical relevance. Depending on their clinical significance, the labelling can be crafted in terms of indications, dosing regimen, contraindications and precautions or simply providing pharmacological information of interest.

Preclinical studies provide some of the earliest opportunities for investigating the potential of an NCE for drug interactions. For example, in an *in vitro* study of the metabolism of one NCE under development, it was demonstrated that the compound had a high affinity towards CYP2D6 and lesser affinity towards CYP2C19 and CYP3A4 in human liver incubations with CYP-specific probe substrates. On this basis, and correlating with *in vivo* concentrations, it was predicted that the compound might cause *in vivo* interaction with CYP2D6-metabolised drugs, whereas interactions with CYP2C19 or CYP3A4 were less probable. This indeed was later shown to be the case in formal *in vivo* studies. Further, it was demonstrated that the compound was principally metabolised by CYP3A4, with lesser contributions from CYP2C19 andCYP2C9. It was therefore predicted that the compound would show considerable interindividual variability and would be susceptible to CYP3A4 inducers and inhibitors. Indeed, these expectations were also confirmed clinically.

Table 5
In vitro approaches to study metabolism of drugs and new chemical entities for the prediction of participation of polymorphic drug metabolising enzymes

In vitro system	Type of *in vitro* information on an NCE	Usefulness/Problems
Human liver microsomes	* Metabolite pattern and routes * Individual enzyme assignment for each metabolic pathway by selective inhibitors or antibodies * Enzyme kinetics * Interaction studies	* Prediction of variability and interactions at an enzyme level * Prediction of role of polymorphisms * Only phase I and UGT enzymes present
Human hepatocytes Human liver slices	* Metabolite pattern and routes as a function of time * Concentration-dependence of metabolism (kinetics)	* Prediction of role of various pathways to kinetic behaviour, especially those catalysed by polymorphic enzymes * The whole liver enzyme complement expressed in living cells
Recombinant human enzymes Other human organ *in vitro* systems	* Metabolite pattern * Enzyme kinetics * Organ/tissue-specific metabolic and enzyme data	* Assignment of individual enzymes in the metabolism * Prediction of kinetic behaviour in patients with specific organ diseases * Prediction of metabolism in target organs
Humanised transgenic animals (actually *in vivo* system)	* Transgene-specific metabolism (and its consequences)	* If a transgene is polymorphic, prediction to what might happen in humans * A single enzyme in a whole-animal incubation matrix
In silico modelling	* Metabolite patterns * Enzymes participating	* Only as alerts for other studies * Quantitative data still largely not possible
Animal hepatic *In vitro* systems	* Metabolite patterns and activities and participating enzymes	* Comparisons between human and animal data (extrapolation problems).

5.2 Clinical studies

In an attempt to explore the role of pharmacogenetics in determining drug response during drug development, genotyping of all subjects and patients participating in clinical trials is being increasingly considered. The obvious examples are drugs with a very narrow therapeutic index. At present, the development cost of an NCE is estimated to be US$ 802 million. The additional cost of genotyping the entire population in a clinical trials programme would be only a very small fraction of the total cost. This is almost certainly a highly cost-effective investment in terms of the useful information relevant to safety and efficacy of the drug but there may be considerable ethical and practical obstacles.

One alternative strategy worth considering is pre-specified post-hoc genotyping (for relevant drug metabolising enzymes and pharmacological targets) and intensive pharmacologic investigations of individuals of specific regulatory interest. This strategy is illustrated in Figure 1. Arguably, as a proactive measure, the protocol of every clinical trial in man could include a section "Variability in drug pharmacokinetics and pharmacodynamics".

5.2.1 Phase I

Early phase I clinical studies should aim at characterising the effect of genotype on the pharmacokinetics of the drug in healthy volunteers. The role of non-genetic factors such as the influence of co-morbidity (such as liver disease) and co-medications (inhibitors or inducers of drug metabolism) should also be explored and the variability from these non-genetic factors should be compared to that due to genetic factors. In order to characterise the true consequences of genetic variability in pharmacokinetics, it is important to investigate not only the interindividual but also the extent of intraindividual variability. This is best done by studies of replicate design in a panel of genotyped healthy volunteers.

Preclinical and *in vitro* studies should have identified the main drug metabolising enzymes and the potential pharmacological targets (responsible for therapeutic as well as toxic effects) of the parent drug and its main metabolites. If any of these are known to be polymorphic, subjects participating in at least one single dose and one multiple dose studies should be appropriately genotyped and the data analysed for association with any genetic influences in pharmacokinetics or pharmacodynamics. Similarly, subjects in drug interaction studies should be genotyped to ascertain the association of the presence or absence of an interaction with any particular genotype. Genetic influences can be modified or genetic effects reproduced by the presence of co-morbidity. For example, inhibition of a drug metabolising enzyme (e.g. CYP2D6 by fluoxetine) produces a poor metaboliser phenocopy despite an extensive metaboliser genotype.

Intensive pharmacology and pharmacogenetic studies are particularly valuable in those subjects who are pharmacokinetic or pharmacodynamic "outliers" in these phase I studies.

5.2.2 Phase II

Following the above phase I studies in healthy volunteers, it may become necessary to investigate the dose-response relationship in phase II studies in genetically defined subgroups of patients.

These studies should be large enough to include the whole range of variability in drug metabolising capacity. If there is any evidence from preclinical and *in vitro* studies of polymorphic pharmacological targets, consideration should be given to at least one concentration-controlled trial in order to address the issues of polymorphisms in pharmacological targets.

By prospective genotyping, phase II studies should aim at ensuring the inclusion of important phenotype/genotype subgroups so as to allow dosing recommendations appropriate to each genotype, rather than a standard dose schedule to suit all. Pharmacogenetic studies may be particularly valuable in those subjects who are "outliers" in these phase II studies – those who show an exaggerated or much attenuated response to a given dose.

The outcomes of phase I and II studies may influence the prospective design of and dose selection for the pivotal phase III studies.

5.2.3 Phase III

These studies are likely to provide the ultimate evidence on the role of pharmacogenetic factors in determining drug response. Patients with unexpected drug response (in terms of efficacy and safety outliers) should be genotyped appropriately for polymorphic drug metabolising enzymes and pharmacological targets. The responses of interest in this context are failure to achieve any therapeutic benefit or development of concentration-related or other serious ADRs. If an association of either response with a genotype is found, the subjects should be studied intensively for pharma-

cology of the drug in these patients. The increased size of the phase III studies will allow a more definitive understanding of the relationship between genotype and drug response to be established and the benefits of a diagnostic test to be evaluated. Phase III studies also provide further opportunities for investigating the role of non-genetic factors in drug response.

In some instances, however, data generated from phase II studies may suggest inclusion or exclusion of a given subpopulation, for example those with a specific genotype, from the subsequent development programme. However, this enrichment design studies have their own unique problems that must be addressed.

5.2.4 Phase IV

Since not all ADRs are detected during the clinical development of a drug, it is vital that there is effective pharmacovigilance system in place throughout the post-marketing period of the drug. Although logistically complex, it may be valuable to collect blood and/or DNA samples from subjects displaying delayed or rare ADRs in phase IV to allow genotyping and to study any unusual features of the pharmacology of the drug in such individuals.

6. Genotyping versus phenotyping

Although the emphasis in pharmacogenetics is on genotyping of patients, phenotyping is a potentially valuable and at times more effective tool. Patients may be phenotyped for their drug metabolising capacity using appropriate substrate drugs as metabolic probes (e.g. dextromethorphan for CYP2D6). Classification of an individual as either an EM or a PM is based on estimation of drug in the serum at a predetermined time point or of the parent drug and its metabolite in urine sample collected over a defined period. The major advantages of genotyping are that it is unnecessary to have a validated assay for measuring the drug in question, no need to administer a probe drug and the lack of interference from interacting drugs that need not be discontinued. For example, in presence of a metabolic inhibitor of CYP2D6, genotyping a patient will correctly identify an EM whereas phenotyping may result in misclassification of an EM as a (phenocopy) PM. For most pharmacological targets, genotyping is at present the only available option to explore the role of genetic factors. Recently, an epinephrine challenge test has been described as a means of establishing an electrocardiographic diagnosis in silent LQT1 mutation carriers.

7. Maximising the application of pharmacogenetics

The value of applying pharmacogenetics in drug development and routine clinical practice is a complex issue.

The presence of a genetic polymorphism(s) in the path between the administration of a drug and response to the drug does not always adversely affect the risk/benefit ratio even in individuals with genetic mutations. These genetic traits may be of less significance for drugs with wide therapeutic index and/or for drugs with metabolites almost as active as the parent drug.

As for genetic influences on drug response, two models exist - high genetic/low environment versus low genetic/high environment. Genes may be categorised into those that have major, moderate and minor effects. References have already been made above to the confounders arising from drug interactions. Furthermore, application of pharmacogenetics will need to carefully consider the nature of toxicities or the consequences of failure of efficacy. This is in addition to the cost-effectiveness of pharmacogenetic testing. The likelihood of preventing a serious reaction makes pharmacogenetic testing an attractive tool provided the frequency of the variant allele has a critical mass frequency within a population.

Above all, one needs to consider how pharmacogenetics will be applied in routine clinical practice. Availability of reliable and rapid genotyping/phenotyping kits together with physician compliance with prescribing information may prove to be the major determinants of the benefits of pharmacogenetics.

8. Conclusions

It is evident that polymorphisms of drug metabolising enzymes have a profound influence on the pharmacokinetics of the drug of interest. Abnormal pharmacokinetics result in unintentional overdosing of those who cannot metabolise the drug. The converse is true with respect to exposure to metabolites that may be therapeutically active. Polymorphisms of pharmacological targets also result in abnormal or supersensitivity to the pharmacological effects from concentrations that are therapeutic concentrations in the majority of the population.

These polymorphisms may have consequences that adversely alter the risk/benefit ratio of the drug in some individuals, that is those with muta-

tions. It is therefore imperative that the possibility of genetic influences should be considered from the earliest stages of drug development.

If the possibility of a genetic influence arises, its qualitative and quantitative implications should then be explored and characterised at every stage of the drug development. This is especially relevant to phase II dose-finding studies and the selection of dose(s) for pivotal phase III studies.

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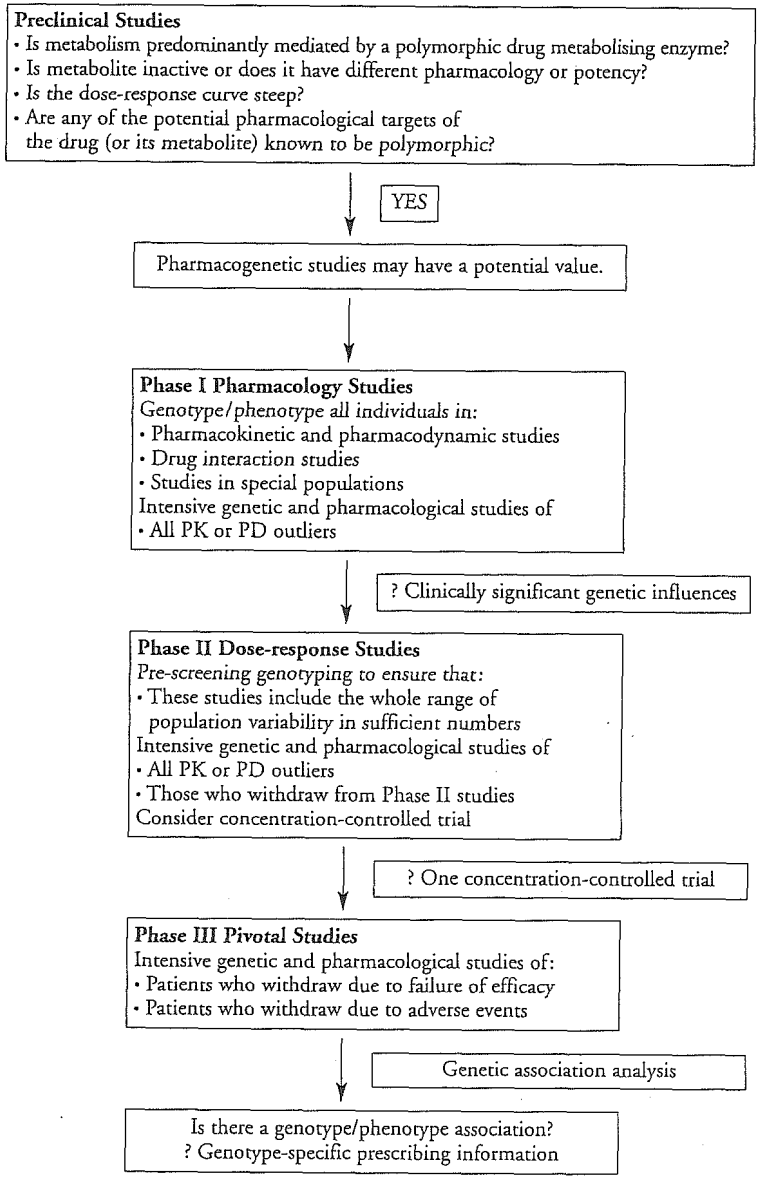
Figure 1
Integrating pharmacogenetics in drug discovery and development



Chapter 5

Impact of Pharmacogenetics on Drug Discovery and Development

1. Introduction

In the last 30 years, the pharmaceutical industry has developed and marketed a large number of medicines that have improved the outcome of many diseases whilst generating significant returns on research and development (R&D) investment for pharmaceutical companies. Over the last 10 years, however, a number of key factors have emerged that impact on the delivery of new medicines to the patient such as:

1. Increase in development costs and time due to greater complexity of clinical development
2. Changing regulatory requirements
3. Increased risk of not getting medicines to market as attrition rates in development are increasing
4. Increased risk of medicines not remaining on the market as safety concerns have caused the withdrawal of a number of medicines in recent years
5. The need to model potential impact on clinical, societal and economic aspects of the treatment to the satisfaction of healthcare providers

The progress and the refinement of research tools, combined with the ever increasing societal demand for safer and more effective medicines, continue to fuel the high cost of development of each new medicine.

Consequently the return-on-investment per drug is decreasing, and perhaps more importantly, the flow of new medicines to patients has gradually diminished. Thus pharmaceutical companies need to use all available tools in order to overcome this situation, with pharmacogenetics currently offering a significant potential. Although still at a basic and experimental stage, pharmacogenetic data are already being submitted to regulatory authorities. A recent CMR survey [1] reported nine companies having experience of submitting applications to the authorities that included pharmacogenetic and pharmacogenomic data, with pharmacogenetic data being included in 4 investigational new drug (IND) applications, 4 clinical trial (CT) applications and 1 new drug application (NDA).

In this chapter, we focus on the contribution of genetic variations to understanding variability in drug response. It is recognised that some of

these opportunities and issues are also applicable to other genomic technologies (e.g. gene or protein expression patterns) but will not be specifically covered in this chapter.

The chapter will identify the key development drivers and hurdles relevant to the implementation of pharmacogenetics in drug development programmes, examining the potential role pharmacogenetics may play in the drug development process. The assumption is that pharmacogenetics will improve patient's treatment by allowing prediction of efficacy and/or safety of some medicines, providing additional claims information and improved prescribing rationale. The discussion will be restricted to considering the impact of pharmacogenetics on clinical drug development (phase I to phase IV), looking at possible requirements for additional and complex development steps that pharmacogenetics may entail, particularly in the short-term, as the technology develops.

Each phase of clinical development will be considered in terms of the potential impact of pharmacogenetics on time, risks and overall pipeline costs. Where possible, analysis will be carried out using benchmark data for a new candidate medicine. More technical aspects of the application of pharmacogenetics in drug development are discussed in Chapter 4 on "Exploring Pharmacogenetics in Drug Discovery and Development".

2. Summary of the current R&D process

For each new drug that is developed, pharmaceutical companies have typically spent an average of $800 million (i.e. R&D spend divided by number of new medicines) and taken about 15 years from discovery in the laboratory to the marketplace. Of this cost, a significant fraction – estimated as approximately 70% – can be attributed to failures along the way – this is a stark statistic of the effect of attrition on utilisation of R&D resources [2].

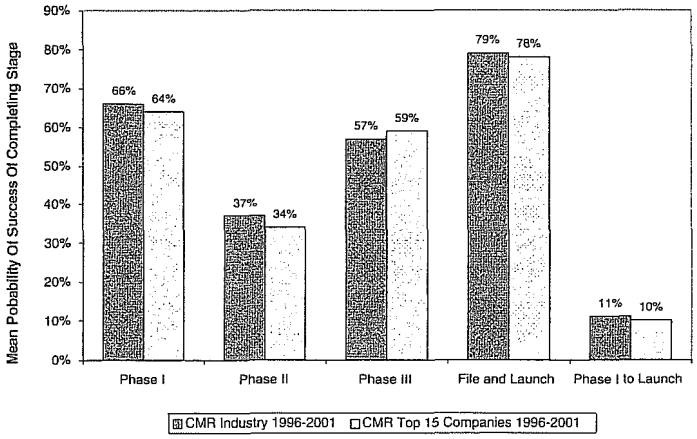
Over the last few decades, it has become progressively more expensive to develop a new chemical entity (NCE) with the cost of developing an average NCE having increased from $138 million in the 1970's through $318 million in the 1980's to $802 million in the late 1990's. This rise is evident even when adjusted for inflation, in part due to increased attrition, and in part due to the requirements for larger and, more complex and multiple clinical programmes [3]. As pharmacogenetics is expected to substantially influence the economics of clinical development, we will focus the discussion particularly on this aspect of R&D. It should also be recognised

that the absolute cost and timing of each development phase will vary depending on the type of product, the disease/therapeutic area/or whether the candidate medicine is a new entity or an approved medicine being developed for a new indication. Therefore, this chapter will concentrate on development costs associated with a new candidate medicine using benchmark data that take into account the costs of the clinical process.

There are various estimates in the literature of the absolute costs of bringing a particular medicine to the market (i.e. the total costs of all the activities on a given candidate medicine), ranging from $250 million to $600 million. Within these figures, the average R&D costs per sector can be broken down into target identification ($165 million), target validation ($205 million), candidate selection ($40 million), lead optimisation ($120 million), preclinical ($90 million) and clinical ($260 million) [4]. These costs are based on all drugs reaching that phase and so include failures. As there are fewer compounds in phase III than in the earlier phases, the contribution of phase III costs to an individual programme is seen to be much higher.

Compounds are lost from drug development at every stage, with less than 10% of compounds entering clinical studies successfully achieving registration and launch. The reasons for attrition can be many and

Figure 1
CMR data based on cohort approach looking at the fate of NCEs entering phase 1996-1998, with progression decision made by 2001 [6]



different in nature and pharmacogenetics cannot be expected to address all areas; but with 10% of drugs failing due to adverse drug reactions (ADRs) in humans, 30% failing due to lack of efficacy and 39% failing due to unfavourable pharmacokinetic and metabolic properties, pharmacogenetics has the potential to influence a significant number [5]. Benchmark data (Figure 1) suggests that project failure is highest in phase II of clinical development with a probability of success (PoS) of approximately 35%, but is also significant in phase III with PoS of about 60%. When one bears in mind the significant cost of the average phase II and phase III development programmes, $40 million and $160 million respectively, the importance of reducing late stage attrition in order to increase the success of developing new medicine becomes clear.

3. Impact of pharmacogenetics on clinical development

Pharmacogenetics seeks to associate genetic variations with differences in response to medicines and the knowledge gained by studying the genetics of pharmacological response can be used to help understand the basis for efficacy and/or safety issues and ultimately to improve the therapeutic outcome for patients [7]. Pharmacogenetics can therefore provide scientific insights into variable response that are difficult – if not impossible – to obtain from the more traditional approaches.

For pharmacogenetics to have a defined application in drug development and a clinical value in prescribing, a marker (or combination of markers) must be found that can predict a difference in response, so that the overall improvement in the benefit/risk ratio of the medicine in a given indication is robust enough to guide the prescribing decision. The criteria for what determines a 'robust' pharmacogenetic marker will depend on the particular therapeutic area and the disease being treated.

Pharmacogenetics is a tool that provides additional information to guide the drug development process, which may provide insights into response related to efficacy and safety, and can be applied in a number of ways to:

- Identify appropriate patient groups
- Stratify patients in clinical studies
- Guide prescribing in clinical practice (which may involve the use of a pharmacogenetic test)
- Provide a feedback into research to identify unmet need (non-responder group)

- Facilitate R&D decision making by supporting more informed discussions
- Guide decision making for compounds that do not meet benefit/risk product profile in a traditionally defined broad ('all comers') population, resulting in focused development in a defined subgroup.

There is a lot of excitement about pharmacogenetics, and the technology has enormous potential to transform both clinical development and the utilisation of medicines. However, it has to be acknowledged that pharmacogenetics is still a fledgling science, and while the expectations are high, the number of real examples – especially the ones that have influenced clinical practice or development decisions – are few and far between. While the extensive literature on cytochrome P450s has established a clear role for pharmacogenetics in understanding pharmacokinetic variability, it remains to be seen how valuable pharmacogenetics will be in providing insights into more complex phenotypes of efficacy and adverse events. The preliminary data are very encouraging. For example, the strong association of SNPs with adverse events to both abacavir [8] and tranilast [9] suggests that genetic variation can be a strong predictor of such phenotypes. However, more examples will be needed to establish that pharmacogenetic analysis is a cost-effective addition to the more established and traditional clinical development pathways.

Thus, the application of pharmacogenetics must be clearly validated within clinical trials in terms of clinical validity, and its relevance demonstrated to the regulators in order to guide labelling. In the final analysis, the utility of pharmacogenetics with respect to the treatment strategies and clinical outcomes will ultimately be confirmed when the drug is on the market and being prescribed.

4. Pharmacogenetics and clinical development process

For pharmacogenetics to influence the development and/or prescription of new medicines, it must be embedded into appropriate phases of clinical development. This does not mean that all drugs will be launched with a pharmacogenetic component – or indeed supported by pharmacogenetic data – but it does mean that, where needed, genetic markers of response (efficacy and/or safety) can be identified and validated, ready for use if required.

In order for pharmacogenetics to fulfil the current expectations of enhanced product delivery by providing better product claims, reducing the cost of development and allowing medicines to reach the market

place more rapidly, the traditional development paradigm will need to be challenged. Considerations around powering, population definition and study duration should be considered. As there are a large number of possible variations in the ways by which pharmacogenetics can be applied to the clinical development process, it is difficult to make broad generalisations about the cost, benefit and impact. This is especially true for the later phases of development, where the application of pharmacogenetics will depend, for example, on exploratory data generated earlier in development.

4.1 Phase I

The overall aims of phase I studies are to establish basic pharmacokinetic parameters (usually in normal volunteers) and to exclude safety concerns that would preclude further development of the compound. It is unusual to obtain information on efficacy in phase I studies (although some surrogate pharmacodynamic information may be generated).

Compounds entering this phase of development have a 65% PoS and are therefore likely to complete this phase unless major issues are identified. The duration of this phase is typically 14 months and costs about $60 million depending on the type of drug, its mechanism of action and the therapeutic area.

Although phase I studies are small and tend to be conducted in human volunteers, the inclusion of pharmacogenetics analysis may be used to:

- explore the basis of unexpected variability in pharmacokinetics
- confirm that the drug acts as anticipated on the relevant target
- confirm the expected elimination (metabolic and/or renal excretory) pathways predicted from *in vitro* studies and their potential consequences
- provide information on safety issues associated with known genetic variants

The main contribution of pharmacogenetics to phase I studies is likely to be insights into pharmacokinetics (or dynamics where appropriate) that allow development decisions to be made with greater confidence. For example, is variable pharmacokinetics due to poor absorption (in which case a new formulation may be needed) or to variable metabolism? In these situations, the properties of a compound are outlined and a decision can be made on the possibility or otherwise of developing the compound without investing time and resource on new formulations.

The inclusion of pharmacogenetics in phase I studies is unlikely to result in a significant change to the timing or cost of the development programme, at least in the short-term. If it becomes necessary to generate extensive pharmacogenetic data as part of the phase I programme, this may cause a delay in proceeding to phase II. However, such extensive genotyping would only result from the identification of a significant issue with the compound, which would of course delay the programme in any event.

4.2 Phase II

The major objective of phase II development is to generate exploratory data on safe and effective doses. On the basis of the data obtained, a decision can be made to proceed to phase III. Compounds entering this phase of development have a 35% PoS, and so this is the phase of development with the highest risk of attrition. The duration of this phase is typically 20 months and costs about $40 million depending on the type of drug, its mechanism of action and the therapeutic area.

The pharmacogenetic objectives of this phase are to generate data on which the choice of dose and optimal enrolment criteria for additional (confirmatory) studies can be made. Phase II studies are larger (100-500 subjects), and are thus capable of generating pharmacogenetic hypotheses for both efficacy and any adverse events. If serious adverse events are sufficiently common during phase II studies to make pharmacogenetic studies feasible, it is highly unlikely that the compound will have an acceptable benefit/risk profile. Thus it is during this phase that pharmacogenetics can potentially play a significant role in understanding attrition, particularly for compounds with variable efficacy.

Like traditional studies, phase II pharmacogenetic studies must be designed to produce enough safety and efficacy data to select the correct dose, but they may also have to be designed to select different doses for different populations/genotypes. Independent of the desired outcome, phase II studies incorporating pharmacogenetics may have to be powered to

1. produce enough safety and efficacy data to fulfil traditional requirements and
2. produce enough data to also support development in pharmacogenetically defined subpopulations or
3. produce enough data to consider developing in one particular pharmacogenetically defined subpopulation only.

Once a genetic marker (or a set of markers) associated with a particular response is identified, different design options can then be considered ranging from additional phase II trials, amendments to ongoing programmes and/or amendment to the planned phase III programme. These design considerations need to take into account whether the development plan will continue along a traditional route (i.e. not using pharmacogenetic data to alter the development programme), an enrichment route (using pharmacogenetic data with possible pre-randomisation genotyping to increase the number of appropriately responding patients in the programme) or a focused route (excluding certain patients likely to show unfavourable response due to either poor efficacy or safety concerns). The final decision will depend on many factors including cost and influence on label claims.

If additional larger clinical phase II trials are required to collate sufficient information on a genetic marker in order to substantiate its relevance for inclusion in phase III trials, this will increase the cost (and possibly the time) of phase II studies. However, this increase may be offset by an increase in PoS in phase III, and in some cases a smaller phase III programme.

At the conclusion of phase II, genetic markers of response (efficacy and/or safety) may not have been identified. In this case, unless there is other supporting information, the clinical development project is more likely to follow the traditional development route, with minimal change in traditional costs or timing.

4.3 Phase III

The primary purpose of phase III studies is to provide the pivotal evidence of efficacy and safety for the purpose of drug registration and to establish efficacy and safety parameters in additional populations/drug regimen conditions. Compounds entering this phase of development have a 60% PoS. The duration of this phase is typically 28 months and costs about $160 million depending on the type of drug, its mechanism of action and the therapeutic area.

The outcomes of including pharmacogenetics into phase III development may range from:

- Confirming the validity and clinical relevance of the genetic marker and focusing development only in a pharmacogenetically defined population (may be most relevant for pharmacogenetic safety markers).

- Confirming the validity and clinical relevance of a genetic marker set whilst still demonstrating utility in a wider population. This would result in a traditional registration package supplemented with additional prescribing information on the role of pharmacogenetics in different subpopulations and potential use of the pharmacogenetic test if available/applicable.
- Showing no differential response (efficacy or safety) and following a traditional development route, resulting in a traditional label. Much has been written about the potential savings the inclusion of pharmacogenetics in phase III may bring. However, in the short-term at least, the incorporation of pharmacogenetics into phase III development may not always fulfil the promise of reduction in sample size and increased speed to market.
- For development programmes using pharmacogenetics for efficacy, a reduction in sample size required will occur when the genetic markers are used to predict efficacy and to select patients recruited into this phase. The magnitude of reduction will be related to the anticipated difference in efficacy between the selected and non-selected groups. This means the larger the efficacy difference between the two groups, the lower the number of subjects required. However, the expected savings in time may be restricted by the 'traditional' study design duration, whilst the cost savings associated with smaller pharmacogenetic trials may be eroded by the need to screen large number of subjects prior to entry, the latter depending on the frequency of the identified pharmacogenetic trait(s) in the general population.
- Another issue relates to the nature of the safety database required: in many phase III programmes, the size of the safety database required will define the scale of the phase III programme, so increased power from an efficacy enriched population cannot be translated into smaller studies. In fact, there is some debate as to whether an adequate safety database may also be required in the patient population not selected, so that an adequate risk/benefit assessment can be made in the non-indicated (or contra-indicated) patient group to safeguard against off-label use that has been predicted to occur with pharmacogenetically supported medicines. This is a critical issue for development of pharmacogenetics and needs to be debated fully [10]. Concerns regarding prescribing of medicines to a 'non-labelled' population should be discussed against the general background of 'off label use' since this is a general issue applicable to most medicines, and not one uniquely related to pharmacogenetics.
- For development programmes using pharmacogenetics with pharmacogenetic markers of efficacy, phase III studies are generally powered to

demonstrate efficacy but they will be required to address safety concerns. If the pharmacogenetic markers are also used to identify subjects at increased risk of a treatment-limiting ADR, then there may be only an insignificant reduction in the number of subjects required, and costs and time may be increased due to the need to screen greater number of subjects than generally warranted in a traditional development.

- For traditional development with a pharmacogenetic subset, response rates in different populations may be seen but may not be large enough, either to be clinically relevant or to warrant different dosing regimens. In such cases, development time may remain the same, but additional patient numbers and costs for genotyping will be incurred when compared to traditional programmes.

At the end of phase III, pharmacogenetic markers of response (safety and/or efficacy) may not have been fully validated. At this point, project leaders will have to decide whether there is enough information for a traditional development package or whether additional work is needed, depending on the rationale chosen when entering phase III.

4.4 Market launch

If pharmacogenetic studies during clinical development have established markers associated with efficacy and/or safety that are included in the label at launch, then the usual activities associated with the launch of a new medicine will also have to include additional information on the pharmacogenetic data and their use. While these further development activities – and their associated costs – are not always defined as R&D costs, they will undoubtedly necessitate additional expenditure. This will be particularly true in the short-term, when practising physicians, healthcare providers and patients will be unfamiliar with pharmacogenetically based prescribing. The potential to utilise these new technologies to support labelling claims may result in a significant competitive and financial advantage, although this will have to be considered on a case-by-case basis taking into account also the clinical benefits from a public health perspective.

One could argue that the long-term success/utility of pharmacogenetically based development/prescribing will be dependent on how these innovative products are marketed and supported. Unless physicians, healthcare providers and patients know how to use these new medicines, and perhaps as importantly, know what to expect if these medicines are used correctly, the promise that pharmacogenetics offers may not be fulfilled.

For these early pharmacogenetically based medicines, additional expenditure in education and product support is inevitable.

4.5 Phase 4

In view of the education and product support needs, phase IV studies may be one of the keys to successful pharmacogenetically based drug development. Traditionally phase IV or post-marketing studies are designed to better understand the utility of a new medicine in a broader population and under real conditions of clinical practice than is possible to study during the normal clinical development. Phase IV studies are much more variable than the pre-registration studies, both in size and complexity (and hence in cost and duration).

The impact of pharmacogenetics on phase IV (in terms of cost, time and risk) will be very dependent upon how pharmacogenetics has been incorporated during development and its contribution to the final label. If a new medicine is launched with pharmacogenetic markers associated with efficacy, phase IV studies will hopefully confirm the applicability of these markers in wider populations, with pharmacoeconomic studies being designed and conducted to substantiate public health benefit on large numbers and longer follow-up.

Like traditional development programmes at the phase IV juncture, a pharmacogenetically enhanced medicinal product could follow any number of different opportunities from continued validation of previously identified pharmacogenetic marker sets through to identification of different genetic subpopulations not indicated in the label. During phase IV, although the refinement and further development of a product's characteristics using pharmacogenetics is a possibility, a more beneficial application of pharmacogenetics may be to enhance post-marketing surveillance, providing insights into the rare adverse events that can only appear in the post-marketing arena and which currently cause medicines to be withdrawn from the market [10, 11]. While this is not strictly part of clinical development, using pharmacogenetics to provide scientific insights into these adverse events could have a significant impact on overall R&D productivity (and hence cost-efficiency), as well as enhancing any risk management plan.

4.6 Phase IV post-marketing surveillance systems

Five hundred and forty eight NCEs were approved from 1975 to 1999. Of these, 56 (10.2%) drugs were labelled with a new black box warning

or were withdrawn from the market. Analysis suggests that the estimated probability of a drug being withdrawn from the market over a 25-year period was 20%. More significantly perhaps, forty-five drugs (8.2%) were marked with one or more black box warnings that were not present when the drug was approved. Sixteen drugs (2.9%) approved between 1975 and 2000 were withdrawn from the market during that period: five had a black box warning prior to approval.

It is estimated that over half of drug withdrawals occur within five years of the product launch [12]. In addition there were 81 labelling changes in the *Physicians Desk Reference* for launched products during 1998-2000. Analysis suggests that over 50% of these changes occurred within seven years following product launch [13].

4.7 Identifying drug-related ADRs in the market place

Usually, only ADRs that occur with a frequency of 0.1-1% or greater will be detected during clinical trials. Since the average cohort at the time of licensing is between 3,000 and 5,000 patients, this will provide little or no data on rare events. One suggestion could be to increase the size of the registration package. However, this will only prolong the development time and cost equation whilst more importantly delaying access for patients to new medicines, since study sizes would need to increase significantly if rare events are to be detected. For example for an event with a frequency of 1 in 10,000, one would need to expose up to 65,000 subjects to the drug before 3 cases with that ADR are observed during the clinical trial [14].

Therefore one needs to consider risk management programmes that can handle these rare events once the drug is in the market. Pharmacogenetics could be used as part of a risk management tool and has the potential to help investigate rare ADRs and if appropriate, allow continued access to the majority of patients who will gain benefit. Pharmacogenetically based surveillance programme could supplement existing post-marketing surveillance and risk management programmes. The ability to associate a particular serious ADR with a pharmacogenetic profile may take a substantial period of time if the event rate is low. This, coupled with the logistics of collecting cases (and controls), will require dialogue between the pharmaceutical companies and the regulators.

5. Development of a pharmacogenetic test

For pharmacogenetics to deliver its promise in the clinic, it is important that testing tools, where they are necessary, are readily available to the physician when he/she considers prescribing the medicine concerned. This paradigm requires that development of the pharmacogenetic assay/test must proceed alongside the pharmaceutical agent. If a test is needed to accompany a drug registration package, then there will be an increased development cost and possible delay to market. The cost and the time delay will be dependent upon such factors as when the pharmacogenetic markers are identified, and whether the test is already available or has to be developed.

Many companies involved in pharmaceutical R&D are not manufacturers of diagnostic agents. Hence the development of the test may have to be contracted out or conducted in partnership (see Chapter 12 on "Unresolved Issues and Barriers to Progress"). One option is outsourcing the development of the analytical tools and hence co-sponsor its clinical validation. Another route is to co-develop the test in-house. The additional financial burden of co-developing a commercially viable pharmacogenetic test "kit" has to be considered alongside the opportunities offered by this approach to enhance the business return of the company by establishing a department specializing in test kits.

However in general, the cost of developing a test, without specific clinical claims attached to it, is small compared to the overall cost of developing a medicine, provided that the development of the test can be accomplished within the same timeframe as the medicine without delaying the launch of the medicine.

6. Investments and distribution of resources and risks in R&D when introducing pharmacogenetics

In order to keep a viable pipeline, the pharmaceutical industry has not only to successfully screen/develop new candidates that might compensate for the attrition rate but also to optimise the investments in clinical development. Pharmacogenetics offers new tools, which are predicted to result in benefits not only from a public health perspective (targeted therapy with optimal efficacy response and reduced ADRs) but also from the financial point of view, providing for the analysis of target variance, a reduction in product attrition during development and a potentially streamlined clinical development.

However, while the above becomes a reality, there are a number of legal, regulatory, societal and technical factors that need to be managed carefully within an appropriate policy framework in order to facilitate a smooth transition towards the full deployment of pharmacogenetics in the development of medicines and medical care. This transition has to be managed at all levels, with a system that is flexible, so that the science of pharmacogenetics develops into a public health and prescribing tool, and is not constrained by inappropriate hurdles.

To integrate pharmacogenetics into drug development, specific investments and choices are necessary at various levels in order to adapt the R&D technology and science framework within a company. For example:

- Delivery of high-throughput, accurate and affordable platforms and genotyping assays
- Computational capability such as bioinformatics, statistical modelling and analysis
- Database construction including tracking systems for maintenance of multiple coding regimens.
- Construction of genetic marker/allelic frequency databases to reference pharmacogenetic variability to support global drug development
- Development of expertise – Pharmacogenetic specialists across R&D

Pharmacogenetic approaches currently employed focus predominantly on candidate genes; that is, genes where an *a priori* hypothesis implies a pharmacogenetics role – for example genes involved in drug metabolism or the pharmacological target. Genome-wide scans are however now being explored. At this time, the utility of this technology has yet to be fully clarified. It is, however, expected to increase significantly the ability to identify clinically relevant pharmacogenetic markers related to variable drug responses, although (currently) at significantly greater cost during development.

There is currently a shortage of real life examples demonstrating the overall effect of pharmacogenetics on drug development costs and PoS. Discussion is reliant on models based on incomplete data. Confirmation of such figures will have to await real examples, and even these may not produce the answers initially, since the first pharmacogenetically based drug development programmes may not have been undertaken in the optimal manner (because this has yet to be determined).

7. Conclusions and recommendations

The need for cost – effectiveness in both R&D expenditure and healthcare budgets, as well as the increased pressures to improve R&D from within the pharmaceutical industry and from the market, are likely to be a powerful driving force behind the application, and validation, of any new technology, including pharmacogenetics.

Pharmacogenetics is a technology that is available now and has multiple potential applications in R&D to help alleviate some of these pressures. In order to fully exploit the potential advantages of pharmacogenetics, it should be appropriately applied over the continuum from early clinical development through to the marketing phase. Although the science of pharmacogenetics has yet to fully deliver its promise, it is still anticipated that with the appropriate application, pharmacogenetics can help reduce the risk of late stage failure and thus mitigate the overall financial burden to the company and promote the availability of safer and effective medicines for patients' treatment. In fact it should be considered that each medicine that failed in development, or shortly after launch, is potentially a missed opportunity either for treatment or for better treatment.

It appears however that at present, the changes in development strategy required to include pharmacogenetic approaches may, in fact, not reduce at all the financial investment required in the short-term for an individual compound. The application of pharmacogenetics to select patients for clinical trials and the impact on trial design parameters – e.g. sample size, time to recruitment of patients needed to demonstrate the required risk/benefit ratio – will inevitably vary according to the molecule, target, pathway, specificity and the unmet medical needs/disease in question. It seems, however, that optimisation of phase II clinical trials might reduce the overall duration or size of some of the late pre-approval clinical studies.

There are good reasons to anticipate that integration of pharmacogenetics into the R&D process may provide in the medium term global financial benefit in view of

- Focused and complementary pipelines
- Overall reduction in the attrition rate, particularly during an advanced stage of clinical development
- Pharmacogenetics may lead to (relatively) minimal increases in the cost of developing a medicine. These increased costs should ultimately be offset by the potential additional value of the medicine; that is, spend-

ing more money for each compound but for a shorter time and with less risks of failure during development and after launch.
- If managed correctly and planned for, pharmacogenetics should not significantly increase the time to market for medicine.

In the current transitional phase, the focus should not simply be on the cost savings during development of an individual medicine developed in this way but also on the overall additional value and utility such a medicine might bring. In addition, the value of knowledge gained during a pharmacogenetically based development programme should not be overlooked. R&D budget might have to account for significant and time-sustained investment, especially when considering concomitant development and validation of a pharmacogenetic test.

Few would disagree that pharmacogenetics has the potential to be a useful tool for providing access to additional development and commercialisation strategies. In order for the potential to be fulfilled, it is recommended that
- Exploration and validation of pharmacogenetic markers be increasingly included as part of the R&D strategy with the aim of reducing the attrition rate both during development and after launch. This will also allow appropriate expertise to be developed.
- Generation and discussion of data between pharmaceutical industry and regulators should continue, with the *Voluntary Genomic Data Submission* (VGDS) to the FDA and *Briefing Sessions* with the EMEA as the recognised routes (see Chapter 7 on "Regulatory Perspectives in Pharmacogenetics")

These recommendations, if implemented, will facilitate the development of the technology in an appropriate and cost-effective manner to maximise the opportunity for pharmacogenetics to deliver healthcare benefit, and also ensure more realistic expectations from the application of pharmacogenetics.

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Chapter 6

Improvements in Existing Therapies

1. Introduction

Despite the spectacular successes achieved in drug therapy during the last century (especially the last five decades), none of the existing therapies is either 100% effective or 100% safe. In fact, it may be that a significant proportion of the patients treated with existing therapies obtain only minimal benefit from them, if any at all. Depending on the therapy and the endpoint used to judge response rate, efficacy can range from 25% to more than 90%. The latter is probably a rare scenario in contrast to the prevailing common perception that drugs are beneficial to everyone who takes them.

Historically, drugs have been developed using a "one-size-fits-all" model, assuming that all adults are the same. In the 1950s, it was observed for the first time that heritable deficiencies in enzymes could result in unexpected and even harmful effects. The research performed during the Korean War demonstrated that 10% of black servicemen became anaemic after a particular antimalarial drug. This effect was very rare among white servicemen. The cause was found to be a variation in the gene expressing the enzyme, glucose-6-phosphate dehydrogenase (G6PD). This variation is common among people of African descent. In the US, it is therefore a practice to test for G6PD deficiency in African Americans before treatment with antimalarials that are known to induce haemolysis. Since then, this type of knowledge has resulted only in either limited clinical application or practical outcomes. However, the wordings of many indications approved by regulatory authorities show that regulators are focused in their intent to ensure a better understanding of the drug exposure-response relationship in order that the dosing recommendations are appropriately defined, with the ultimate goal of maximising the risk/benefit ratio. A result of this is a clear trend for drug labels to specify those subgroups of patients likely to respond positively, or negatively, to a particular drug treatment.

The term '*existing therapies*' is used in this chapter to mean all medicines, whether under patent or not, that have already been approved by competent authorities (drug regulatory authorities) for the prevention or treatment of a defined disease/indication in humans. This means that it covers both multi-source pharmaceutical products ('generics') and products

manufactured by originators which may or may not be covered by patent protection ('innovators'). In certain cases it is also extended to the products that have been withdrawn after approval from one or all markets, or to the products for which the originator has applied for, but not yet received, a marketing authorization.

Medicines are approved for marketing based on the analysis of safety and efficacy data obtained during their development in a defined population, along with a comparison against existing therapies as well as against placebo when appropriate. The justification for continued use of existing therapies is, in many cases, the lack of more effective and safer alternatives. This has led to the acknowledgement that in general, the net outcome of existing therapies in certain populations is positive. However, this does not mean that all individuals treated benefit from the treatment and/or none suffers from adverse drug reactions, some of which may be potentially fatal. Moreover, certain patients may not benefit at all from an existing therapy but may nevertheless suffer serious adverse effects. For example:

1. Depending on the ability to acetylate isoniazid, a population can be divided into two phenotypes – slow and rapid acetylators. Rapid acetylators are at risk of potential failure of efficacy against tuberculosis while slow acetylators are at risk of neuropathy. Recognition about the mechanism of isoniazid-induced neuropathy has resulted in vitamin B6 supplementation in slow acetylators. By doing so, this neuropathy is now virtually eliminated. Moreover, failure of treatment is only seen in rapid acetylators if the drug is given on a twice-weekly basis.
2. The efficacy of low dose acetylsalicylic acid (ASA) (75-325 mg) in secondary prevention of thrombotic cardiovascular or cerebrovascular disease is well known. In many countries, it is also approved for primary prevention of vascular events of coronary heart disease. Today, it is possibly premature to suggest that all patients with the appropriate indications will benefit equally from the use of low dose ASA as the risk of low dose ASA itself may lead to increased risk of potentially fatal gastro-intestinal haemorrhage or haemorrhagic stroke. The possibility remains that ASA is prescribed today to many patients who may not benefit from its use but may well be at risk of serious side effects. It remains to be elucidated if pharmacogenetics can offer feasible solutions for better targeting of patients with this extremely cost-effective treatment.
3. Pharmacogenetics may help to reduce the risks associated with the use of angiotensin converting enzyme (ACE) inhibitors, a class of drugs that are now used increasingly and widely for a variety of indications.

It is estimated that currently 35-40 million people are treated worldwide [1]. These agents have been shown to be highly efficacious in the treatment of a variety of life-threatening diseases including congestive heart failure (CHF) and myocardial infarction. There is no doubt that this group of drugs can potentially save millions of lives worldwide if there was access to them. Some ACE inhibitors are already out of patent in a number of countries; others are following. However, even in developed countries, only 21-36% of the patients with CHF are treated with ACE inhibitors [2-4] and over 40% of them discontinue the drug within 6 months of starting therapy [2]. There is a clear need to identify in advance which individuals can benefit from ACE inhibitors with minimal risk of serious side effects. Angio-oedema is a well-known side effect of ACE inhibitors, with the reported incidence of 0.1-0.2% that is probably an underestimate [5]. Black people using ACE inhibitors are at a 3-fold higher risk of side effects and experience higher rates of fatal events [6, 7]. However, determining the true incidence of angio-oedema may require monitoring all patients, not just those already identified as being at increased risk, for this potentially serious side effect. If pharmacogenetics can offer tests with high predictability, patients at increased risk for angio-oedema could be switched to the alternative class of medicines instead; thus avoiding extra costs arising from monitoring of patients and from the resulting morbidity and mortality. The benefits may well outweigh the costs of predictive tests.

2. What can pharmacogenetics offer for existing therapies?

Interindividual variation in response to drugs is a substantial clinical problem. The variation in drug response ranges from failure to respond to adverse drug reactions and drug-drug interactions when several drugs are taken concomitantly. The clinical consequences can be catastrophic. A US study estimated that 106,000 patients die and 2.2 million are injured each year by adverse reactions to prescribed drugs [8]. Pharmacogenetics may reduce the guesswork in prescribing existing medicines, increasing the likelihood of prescribing the right drug, at the right dose, to the right patient at the outset of therapeutic intervention. It may reduce considerably the time, efforts and resources wasted in finding by trial-and-error the correct treatment regimen. Avoiding prescribing medicines to potential 'non-responders' and/or those likely to develop an adverse drug reaction can result in better targeted, or even individualised, pharmacotherapy.