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

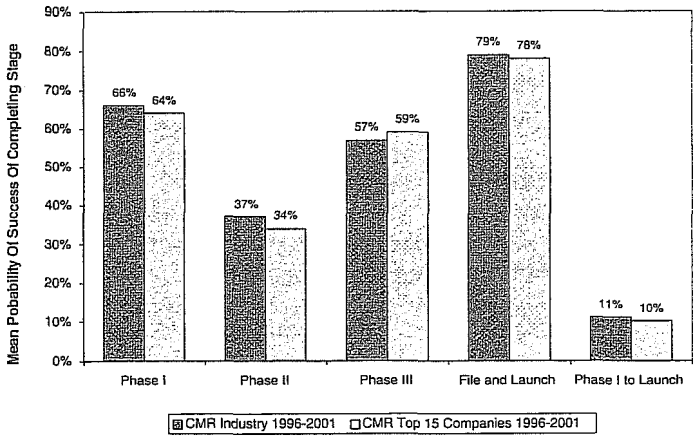


that the absolute cost and timing of each development phase will vary depending on the type of product, the disease/therapeutic area/or whether the candidate medicine is a new entity or an approved medicine being developed for a new indication. Therefore, this chapter will concentrate on development 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.

Typically, a physician prescribes the recommended medicines in the average recommended dosage to his or her patient. If the medicine does not work, and the drug is approved for a range of doses, the physician may try a different dose or may switch to an alternative treatment. Time and money are wasted from unnecessary visits to the physician and the cost for ineffective medicine(s) either used or remaining unused (usually cannot be resold). It is becoming increasingly evident that much of the interindividual variation in response to drugs is inherited and it is clear that not all patients who appear to have the same indication benefit from the treatment. Whereas there are some estimates of the magnitude of the problem arising from adverse drug reactions, there is hardly any systematic prospective information on the scale of the problem arising from treatment failure. There are no well-controlled studies to demonstrate how ineffective many of the well-established therapies are. How many years and how many patients does one need to treat with "statins" to avoid one death from cardiovascular disease? Estimates available suggest certainly more than 10 patients for at least two years per one death avoided. If it were possible to predict with very high probability in which individuals these lipid-lowering drugs do not work at all (this may or may not be the case), not only would there accrue an enormous savings in resources but also many patients would be spared unrealistic high expectations of benefit. These patients may well benefit from alternative potentially effective treatments that may work for them.

## 3. Polymorphisms and the human genome

With recent advances in molecular genetics and genome sequencing, pharmacogenetic research has attracted enormous attention from both the scientific communities and the public. This is due to new technologies that permit rapid screening for specific polymorphisms, as well as recently gained knowledge of the genetic sequences of target genes such as those coding for enzymes, receptors, ion channels, and other types of pharmacological targets involved in drug response. As a result of the completion of the Human Genome Project and other public initiatives such as The SNP Consortium (single nucleotide polymorphisms, see http://snp.cshl.org), comprehensive maps of the human genome have been established including information on genetic variations associated with disease susceptibility as well as pharmacokinetics and pharmacodynamics. However, in general, identification of single nucleotide polymorphisms is ahead of the clinically more important task of correlating genotypes with phenotypes.





Research in pharmacogenomics and pharmacogenetics is developing in two main directions: firstly, identifying specific genes and gene products associated with various diseases which may act as targets for new drugs and/or diagnostic tools and, secondly, identifying genes and allelic variants of genes that affect the response to drug therapies.

Increasing numbers of research programmes have evolved from the Human Genome Project, including genome-wide screens to identify differences between individuals that arise from a single base pair alteration in their DNA or single nucleotide polymorphisms (SNPs). SNPs can be used to map and identify specific genes associated with various diseases such as cancer, diabetes, and arthritis. Many of the proteins encoded by these genes are expected to be new targets for drug therapy but may also improve our diagnostic capabilities and help to stratify otherwise heterogeneous diagnostic groups into more precise subgroups that may have different responses to the existing therapies. The fact that these genes were identified by polymorphism analysis indicates that drugs directed at such targets may have different effects in different patients. This leads to the concept of drug stratification or individualised drug treatment, in which the choice of drug, or the dose of a drug, is influenced by a patient's genetic status.

Genomic analysis has generated an enormous amount of information on human polymorphisms. There are over 4 million single nucleotide polymorphisms in public databases and more will probably be identified over the next few years. However, a greater challenge will be to determine the function of each polymorphic gene or, to be more exact, of the gene product and its variant forms. It should be noted however, that it might not always be necessary to know the function of a polymorphism as it relates to clinical utility. This is often seen in many drug development programmes, where compounds progress to demonstrate clinical utility, without its mode of action having been elucidated. In some circumstances, it may be necessary to determine the functional significance of a gene product for its toxicological importance and whether individual allelic variants are of therapeutic importance. Such expression and function profiling studies that enables the testing of genotype-phenotype correlations are expected to be extremely important for further advances in the field of pharmacogenetics.

In terms of current clinical practice, it is more relevant to determine individual genetic variations that will improve both the efficacy and safety of existing therapies. Because a relatively large number of patients receiving

a drug fail to gain the expected benefit, pharmacogenetics may identify the reasons for lack of benefit in certain individuals. However, adverse reactions are a major societal and economic healthcare problem and patients are more concerned about drugs doing harm to them. Therefore, the overall impact of pharmacogenetics in improving safety is equally important, if not more than in improving efficacy. Polymorphism in any one of many genes including those encoding drug receptors, drug transporters, and cell signalling pathways can be important factors in determining clinical response. It appears that among the polymorphisms of clinical relevance and of immediate utility are those involved in drug metabolism and disposition (e.g. CYP2D6, TPMT).

Functional polymorphisms in any one of these genes can lead to either a lack of therapeutic effect, unexpected clinical responses or an adverse reaction (Table 1).

**Table 1**
**Potential effects of polymorphic drug metabolism on drug treatment**

| |
|---|
| 1. Adverse drug reactions |
| 2. Extended pharmacological effect |
| 3. Lack of prodrug activation |
| 4. Metabolism by alternative, deleterious pathways |
| 5. Ultrarapid metabolism (e.g. duplicated CYP2D6) |
| 6. Modification of drug-drug interactions |

The reader is referred to Chapters 2 and 3 on "Abnormal Drug Response" for additional discussions.

Polymorphisms have now been identified in more than 20 human drug metabolising enzymes, several with substantial inter-ethnic differences in their frequencies. The phenotypic consequences of some of these are critical determinants of therapeutic outcome [9-13]. Important examples are polymorphisms in the cytochrome P450 enzymes and in thiopurine S-methyltransferase (TPMT).

### 3.1 Cytochrome P450 drug metabolising enzymes

The cytochrome P450 drug metabolising enzymes (frequently referred to as CYP isoforms) are a multi-gene family of enzymes found predominantly in the liver (but present also in other tissues such as the brain). They are responsible for the metabolic elimination of a vast majority of





the drugs currently used in medicine. Genetically determined variability in the level of expression or function of some of these enzymes has a profound effect on drug response. In 'poor metabolisers' the genes encoding specific cytochrome P450s often contain inactivating mutations, which result in a complete lack of active enzyme and a severely compromised ability to metabolise drugs.

Thus, mutations in the gene encoding cytochrome CYP2D6 (known previously as debrisoquine hydroxylase) give rise to distinct phenotypes in a population – extensive and poor metabolisers. Case reports suggest that this polymorphism has clinical consequences for some individuals (see Chapter 3 on "Abnormal Drug Response"). Polymorphism not only affects drug disposition but can also be important in the conversion of prodrugs to their active form. Codeine is an old and widely used pro-analgesic that is metabolised to the analgesic morphine by CYP2D6, and the desired analgesic effect is not achieved in CYP2D6 poor metabolisers. CYP2D6 is highly polymorphic and is inactive or dysfunctional in about 6-9% of Caucasians of white origin [14]. Thus, millions of people worldwide may be potentially at risk of compromised metabolism or adverse drug reactions when prescribed drugs that are CYP2D6 substrates. Many CYP2D6 substrate drugs are used for treating chronic illnesses such as psychiatric, neurological, and cardiovascular diseases (Table 2). They have a narrow therapeutic window, commonly have side effects and are intended for long-term administration. Clinical problems can also arise from the co-administration of drugs that inhibit CYP2D6 or compete with its other substrate(s). A drug may interact with and inhibit CYP2D6 to the extent that the enzyme is no longer functionally active, resulting in a patient responding like a poor metaboliser even though he or she has an 'extensive metaboliser' genotype. Thus, quinidine, a powerful CYP2D6 inhibitor, may exaggerate the effects of other CYP2D6-metabolised drugs that are prescribed concomitantly or may prevent the metabolic activation of drugs such as codeine by CYP2D6.

Another variant results from amplification of the entire CYP2D6 gene, with some individuals inheriting up to 13 copies of the gene, arranged in tandem [15]. This amplification polymorphism results in affected people metabolising drugs that are CYP2D6 substrates so quickly that a therapeutic effect cannot be obtained at conventional doses. For example, it has been estimated that, while a daily dose of 10-20 mg nortriptyline would be sufficient for a patient who is a CYP2D6 poor metaboliser, an 'ultrarapid metaboliser' inheriting multiple copies of the gene could require as much as 500 mg a day [16]. These individuals develop rapidly accumu-

Table 2
Examples of drugs that are substrates of cytochrome P450 CYP2D6

| Cardiovascular drugs | Neuro-psychiatric drugs | Analgesics | Miscellaneous |
|---|---|---|---|
| Alprenolol | Amitriptyline | Codeine | Atomoxetine |
| Bufuralol | Clomipramine | Hydrocodon | Chlorpheniramine |
| Carvedilol | Desipramine | Oxycodon | Dexfenfluramine |
| Encainde | Doxepin | Tramadol | Dextromethorphan |
| Flecainide | Duloxetine | | Methadone |
| Indoramin | Fluoxetine | | MDMA ("ecstasy") |
| Metoprolol | Haloperidol | | Phenformin |
| Mexiletine | Imipramine | | Sparteine |
| Nebivolol | Levomepromazine | | Tolterodine |
| Oxprenolol | Maprotiline | | Traxoprodil |
| Perhexiline | Mianserin | | Tropisetron |
| Propafenone | Nortriptyline | | |
| Propranolol | Paroxetine | | |
| Timolol | Perphenazine | | |
| | Risperidone | | |
| | Sertindole | | |
| | Thioridazine | | |
| | Trimipramine | | |
| | Venlafaxine | | |
| | Zuclopenthixol | | |

lating metabolites that may prove toxic. For example, ultrarapid metaboliser may experience morphine toxicity following administration of codeine [17].

CYP2C9 is another member of the cytochrome P450 superfamily, which metabolises warfarin and phenytoin. Its activity influences patients' response to these well established drugs with narrow therapeutic index and their dose requirements [18-20].

### 3.2 Thiopurine S-methyltransferase

Another clinically important polymorphism occurs in the enzyme thiopurine S-methyltransferase (TPMT) [21, 22] that is responsible for the metabolism of the antitumour agents, azathioprine, 6-mercaptopurine and 6-thioguanine. Genetic mutations at the locus expressing this enzyme are associated with difficulty in avoiding toxicity whilst trying to achieve an effective concentration of these drugs in children with childhood acute lymphoblastic leukaemia [23]. Children with inherited TPMT deficiency exhibit severe haemopoietic toxicity when exposed to normal doses of drugs such as 6-mercaptopurine, whereas those with a high activity form of the enzyme require high doses of the drug to achieve any clinical benefit. TPMT polymorphism is relatively rare, with only about 1% of the white population being homozygous for it, but, since these individuals show exaggerated toxic responses to normal doses of these drugs, TPMT phenotype may be an important factor in the successful treatment of childhood leukaemia. Some centres already provide a diagnostic genotyping or phenotyping service to guide the clinical use of 6-mercaptopurine and azathioprine.

Other major polymorphic drug metabolising enzymes, including members of the cytochrome P450 family and phase II conjugating enzymes, have been recently reviewed [10].

### 3.3 Genetic polymorphisms and their potential for improving existing therapies

The following is a brief list of receptor and enzyme polymorphisms that are likely to affect response to existing therapies (selected examples of clinically important polymorphisms)

1. ß1-and ß2-adrenoreceptors
2. Angiotensin-converting enzyme (ACE)
3. Serotonin transporter (5-HTT)
4. 5-lipoxygenase (ALOX-5)
5. Cytochrome P450 enzymes (e.g. CYP2D6, CYP2C9, CYP2C19)
6. N-acetyltransferase 2 (NAT2)
7. Dihydropyrimidine dehydrogenase (DPD)
8. Cholesteryl ester transfer protein (CETP)
9. Multi-drug resistance protein (MDR-1) (P-glycoprotein)
10. Thiopurine S-methyltransferase (TPMT)
11. Leukotriene synthesising enzymes and receptor polymorphisms.

## 4. The current situation

Pharmacogenetic testing is currently used in a relatively limited number of teaching hospitals and specialist academic centres. The widely practised application of pharmacogenetic testing is the use of CYP2D6 genotyping to aid individual dose selection for drugs used to treat psychiatric illness.

Several independent testing laboratories have started to provide the pharmaceutical industry and medical practice with a high throughput, DNA-

based, testing service for a range of pharmacogenetic polymorphisms. It is, however, difficult to predict to what extent the pharmaceutical industry will routinely incorporate pharmacogenetic testing into prescribing schedules for drugs that are subject to polymorphic metabolism. This will depend to some extent on the attitude of the drug regulatory authorities. The reader is referred to Chapter 7 on "Regulatory Perspectives in Pharmacogenetics".

The clinical applicability and cost-effectiveness of pharmacogenetic testing depends on the relative importance of each polymorphism in determining therapeutic outcome. Physicians need to be aware of whether a drug they are prescribing is subject to pharmacogenetic variability and know how to use this knowledge. In addition, a reliable, DNA based, testing service needs to be made available. Pre-treatment genotyping may allow a more appropriate choice and doses of specific drugs, particularly those for treating psychiatric disorders. At present, adverse drug reactions occur in a substantial proportion of patients: a recent US study showed that, in patients prescribed psychiatric drugs that are CYP2D6 substrates, adverse drug reactions were observed in every patient with inherited mutations inactivating the CYP2D6 gene [24]. Others have questioned whether genotyping for CYP2D6 alone has much to offer in safe and effective use of neuroleptic drugs [25]. Nevertheless, Kirchheiner et al have provided a preliminary guidance for a number of drugs metabolised by CYP2D6 and CYP2C19 with a view to introducing genotype/phenotype-specific dose schedules [26].

## 5. The future

Pharmacogenetics is still an evolving discipline where for certain pharmacogenetic tests, there is ample mechanistic and epidemiological evidence demonstrating their value in improving risk/benefit. For other pharmacogenetic tests, the evidence is only suggestive, but not definitive, of clinical value. We are still a long way from having a pharmacogenetic DNA chip that general practitioners can use to identify all the drugs (or doses of a drug) to which any particular patient is responsive, non-responsive or intolerant.

However, there is increasing evidence that pharmacogenetics may become a valuable tool in health service. One day it may be considered unethical not to carry out such tests routinely to avoid exposing individuals to doses of drugs that could be ineffective or even harmful to them. The ability to identify sensitive individuals, either before drug treatment or after an adverse





drug response, would also be of economic importance as it would avoid the empiricism associated with matching the most appropriate drug at its optimal dose for each patient. It might also substantially reduce the need for hospitalisation, and its associated costs, because of adverse drug reactions.

Increase in knowledge of the mechanisms of drug action, identification of new drug targets and understanding of genetic factors that determine the response to drugs may allow us to design drugs that are specifically targeted towards particular responder populations, avoiding genetic variability in therapeutic response. The extent of genetic polymorphisms in the human population indicates that pharmacogenetic variability will probably be an issue for most new drugs.

The development of pharmacogenetics provides at least one mechanism for taking drug prescription away from its current empiricism and progressing towards a more patient-tailored 'individualised' drug treatment. Already, in the UK, the Department of Health has initiated an innovative GB£4 million start-up funding scheme for supporting research aimed at exploring the role of pharmacogenetics in improving existing therapies that patients are commonly taking now or are likely to be taking soon [27]. Proposals could involve the development of new services or new roles in existing therapies and applications for funding closed on 25 February 2004 [see http://www.doh.gov.uk/genetics/servicedev.htm] and six research projects investigating the value of pharmacogenetics in improving existing therapies have been funded.

### 5.1 Predicted developments

1. Changes in product information. Prescribing advice will start to relate dose to genotype and will highlight the possibility of drug interactions when multiple drugs are prescribed concomitantly.
2. Step-wise creation and implementation of prescribing guidelines, based on clinical studies, for drugs that are subject to substantial polymorphic metabolism.
3. Establishing and recording of individual patient genotypes and phenotypes i.e. 'personal pharmacogenetic expression profiles' as part of medical records.
4. Implementing pharmacogenetic testing may substantially reduce the need for hospitalisation following the use of existing therapies, and its associated costs, because of reduction in adverse drug reactions.
5. More public funds channelled to research concerning existing therapies as outcomes may save considerable public spending on existing drugs,

unlock finances for the development of new therapies and achieve better health outcomes for the populations.

*Anticipated benefits of pharmacogenetics and pharmacogenomics for existing treatments:*

1. Improving rational drug use and possible wider access to medicine – identify people most likely to respond to certain drugs and avoid using these drugs in those who may be at risk of serious adverse drug reactions
2. Reviewing for use in specific subgroup of patients those drugs that have been withdrawn and expanding indications for drugs already on the market
3. Step-wise elimination of "trial-and-error" or "one-size-fits-all" approach to prescribing
4. Saving resources.

## 5.2 Limitations and challenges

1. Motivation to fund research related to existing therapies may be low and compete with motivation to invest into new therapies
2. Public acceptance of genetic profiling may need time
3. For existing medicines, access to more targeted prescribing approach may be too costly to attract funds
4. Distinguishing environmental factors from genetic factors may be more difficult than expected and cause failure to achieve better treatment outcomes with pharmacogenetic approach
5. For existing medicine, complexities of interactions with drugs and other types of health products may not have been investigated and may complicate pharmacogenetic targeting approach.
6. Pharmacogenetic targeting may raise ethical issues that need to be identified and discussed (see Chapter 9 on "Ethical Issues").

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# Chapter 7
# Regulatory Perspectives in Pharmacogenetics

## 1. Introduction and background

Environmental and genetic factors, together with therapeutic interventions are the major determinants of public health. The sequencing of the human genome and the development of genetic and genomic technologies promise to improve public health and the economics of healthcare. The technologies can provide knowledge of how pharmacogenetic and pharmacogenomic information can be used to optimise the risk/benefit of many drugs and reduce the incidence of adverse drug reactions.

There is a diversity of opinion regarding the definitions of *pharmacogenetics* and *pharmacogenomics*. *Pharmacogenetics* is defined as the study of interindividual variations in DNA sequence related to drug disposition (pharmacokinetics) or drug action (pharmacodynamics) that can influence clinical response. For example, polymorphic variations in the genes that encode the functions of drug metabolising enzymes, transporters, ion channels and receptors can result in wide interindividual differences in the dose-plasma concentration-response relationships for many important therapeutic agents. Pharmacogenetic studies include applications of single gene sequences or a set of multiple gene sequences to investigate variations in DNA sequence that may influence drug response. In contrast, *pharmacogenomics* is defined more broadly as the application of genomic technologies to elucidate disease susceptibility, drug discovery, pharmacological function, drug disposition and therapeutic response. In this context, pharmacogenomic studies include a whole spectrum of markers ranging from genome-wide scans, single nucleotide polymorphisms (SNP), candidate genes, haplotype markers and alterations in gene expression or inactivation that show promise to be predictive of drug action. Moreover, integrating pharmacogenetic and pharmacogenomic information following recent progress in human genetics and genomics has given new insights into (a) the basis for heterogeneity in disease states (e.g. subtypes of breast cancer), (b) predictive medicine (e.g. risk of developing or preventing Alzheimer's disease) and (c) dosage regimen selection for subgroups of patients (e.g. poor and extensive metabolisers of a drug metabolised by CYP2D6). Pharmacogenetics and pharmacogenomics promise to improve our understanding of the natural interindividual variability in disease susceptibility and drug response and have the potential to improve drug development and therapeutics in the future.

## 2. Drug development and regulatory assessment

Genome-based technologies have become more readily available, cost effective and reliable. As a result, pharmaceutical companies today are collecting pharmacogenetic or pharmacogenomic data in an increasing number of early and late clinical drug trials. However, many of these applications in drug development are exploratory and in most cases it is not yet apparent how to determine *a priori* how individuals would respond to a drug. Thus, there are only a few cases where pharmacogenetic or pharmacogenomic data have been incorporated into registration applications as a confirmatory test. In the future however, as our knowledge of hereditary factors and other determinants of drug response evolve, it is anticipated that the drug development process will lead to regulatory assessment, approval and marketing of drugs that would be genetically driven and individually tailored for optimal response.

The current regulatory framework in terms of guidelines that already recommend the sponsors of new drugs to explore pharmacogenetic influences during drug development and in terms of labeling of some drugs is described in Chapter 4 on "Exploring Pharmacogenetics in Drug Discovery and Development".

Regulatory agencies have the dual responsibility of protecting public health by assessing the risk/benefit, doses and dosing regimens of drugs and of promoting efficient and optimal drug development. Regulatory authorities worldwide share a common goal with the pharmaceutical industry to make available drugs that are effective, relatively free of serious adverse events, and have acceptable risk/benefit ratios. Thus, regulatory agencies and the pharmaceutical industry should encourage and facilitate exploration and utilization of pharmacogenetics and pharmacogenomics in the drug development process when and where it can make a perceptible difference in the practice of medicine.

There are three broad components of public health and drug therapy that are related to the use of pharmacogenetics and pharmacogenomics and are of interest to regulatory authorities:

### 2.1 Drug efficacy and effectiveness

Pharmacogenetic and pharmacogenomic data can be used to identify drug targets for specific subsets of a disease, or to identify a responder (or non-responder) to a drug in advance and thereby reduce the risk of therapeutic failure.





### 2.2 Drug safety and adverse events

Pharmacogenetic and pharmacogenomic data can be used to identify *a priori* subsets of the target patient population who are at greater risk of developing a drug-related adverse event, and thereby reduce the frequency of adverse reactions.

### 2.3 Drug dose and dosing regimens

Pharmacogenetic and pharmacogenomic data can be used to identify, prior to prescribing a drug, an appropriate dose for different subsets of patients that would improve the risk/benefit of the drug in these subsets in order to individually optimise therapy.

Thus, in many ways, regulatory agencies believe that pharmacogenetics and pharmacogenomics may provide a more effective tool in risk management.

## 3. The Pharmacogenetic/pharmacogenomic paradigm

The general approach to applying pharmacogenetics or pharmacogenomics in drug development is likely to be a three-step process.

### 3.1 Selection of a target disease or drug candidate

Usually the target disease is a common one whose pathophysiology is heterogeneous and where drug effects on clinical endpoints are highly variable between patients but where variability in response, for the most part, is unrelated to environmental or life-style factors. The candidate drug is likely to be one of several therapies available for a disease and its site and mechanism of action are well characterised.

### 3.2 Development of a predictive pharmacogenetic or pharmacogenomic test

The pharmacogenetic test usually is based on genetic variation in one or more biomarkers as evidenced by SNP or haplotypes, by basal gene expression levels (e.g. mRNA levels) or by predictive expression patterns in target pathogenic tissue (e.g. tumours), or in host tissue. The test is likely to predict responsive disease subsets of patients, the risk of disease progression or the likelihood of achieving efficacy, having adverse events or improving the selection of the dose of a drug for a given patient.

### 3.3 Determination of the analytical validity, clinical validity and clinical utility of a predictive pharmacogenetic or pharmacogenomic test

The analytical validity defines the accuracy and precision of the pharmacogenetic or pharmacogenomic test in measuring the genotype of interest. It is often expressed as analytical sensitivity and specificity and the performance of the test is commonly compared to a "gold standard".

The clinical validity describes how good the test is in predicting clinical outcome. It is frequently characterised as the clinical sensitivity and positive or negative predictive values of the pharmacogenetic or pharmacogenomic test for biomarkers of drug efficacy or safety. In order to establish clinical validity, the biomarkers may be identified early and determined later in clinical trials involving patients with the target disease that may develop an adverse reaction, or fail to respond to therapy. This often involves stratification of patient enrolment in clinical trials.

The clinical utility of a positive or negative pharmacogenetic or pharmacogenomic test determines how good the test and associated interventions are in improving health and/or preventing disease. The most rigorous assessment of clinical utility is through randomised, controlled clinical trials in which patients are randomly assigned to different interventions based on the results of the test.

## 4. Limitations and challenges of pharmacogenetics and pharmacogenomics

It is important that industry and regulatory authorities recognise the major limitations and challenges of using pharmacogenetic and pharmacogenomic information in clinical trials. Predictive pharmacogenetic and pharmacogenomic tests are complex in that their utility may be related to either disease biology (defining something about a patient's current or future disease condition) or drug response (defining the probability or likelihood of a clinical outcome both desirable and undesirable).

The limitations and challenges include the following:

- Patient populations are genetically heterogeneous; the phenotypes of the same common diseases, or many diseases with unmet medical need, are the result of complex interactions between genetic traits, and in some cases, the environment





- Because of population heterogeneity, a pharmacogenetic or pharmacogenomic test may identify only a small proportion of patients in which inherited mutations at one or more gene loci contribute significantly to the disease phenotype. This may lead to orphan drug status for an intervention; however, the threshold for an orphan drug differs between countries.
- Responses to drugs are highly variable between subjects, and are influenced by multiple genetic factors as well as non-genetic covariates such as drug interactions or co-morbidities
- Careful consideration must be given to the clinical and regulatory criteria in defining useful genotype-phenotype associations
- There is a need to develop efficient study designs and to adapt statistical methods and information technology paradigms for the accrual, analyses and reporting of pharmacogenetic/pharmacogenomic data

## 5. Current situation

At present, there are few examples of pharmacogenetic or pharmacogenomic predictive or diagnostic tests that have been approved by a regulatory agency for the purpose of individualising therapy.

Among the few exceptions are the immunohistochemical and DNA-based tests respectively to detect tumour HER-2 over expression in women with breast cancer who would benefit from trastuzumab (Herceptin® Roche), and the use of viral DNA tests to determine the level of drug resistance in patients that are HIV positive as an aid in the selection of a protease inhibitor. To date, much of the discussion between the pharmaceutical industry and regulatory agencies about pharmacogenetics and pharmacogenomics has focused on issues relating to emerging regulatory policy with respect to the validity, predictability, and usefulness of pharmacogenetic and pharmacogenomic data. In many ways, the development and use of pharmacogenetic or pharmacogenomic tests represent an "enrichment" tool for characterising safety or efficacy in clinical trials. Enrichment of target populations in drug development for efficacy promises to allow studies to be smaller and more efficient by excluding the enrolment of non-responders. However, one of the major unresolved concerns is how sufficient safety data will be acquired on a new drug when genotyping for efficacy is used to select patients for enrolment in a pharmacogenetic/pharmacogenomic clinical trial. Applications of pharmacogenetics/pharmacogenomics in the post-marketing surveillance setting may provide options for addressing this concern.

While inclusion or exclusion of particular genotypes or phenotypes (e.g. particular protein or mRNA expression patterns) is similar to other forms of enrichment that are well known to regulatory agencies and industry, there are several short-term considerations for regulatory agencies and the pharmaceutical industry as delineated below:

- Regulatory agencies worldwide have formed internal working groups to focus on issues of pharmacogenetics and pharmacogenomics with the intent of increasing an understanding of the science and to consider the need and feasibility of regulatory guidances or guidelines for industry. The achievement of a harmonised approach to pharmacogenetic/pharmacogenomic data is highly desirable to facilitate global consistency in the use of such data in drug development and regulatory assessment.
- Regulatory scientists anticipate seeing greater use of cytochrome P450-based genotype tests in drug development. This would lead to more information on the use and value of such tests in product information; for example to characterise clinical trial population into extensive and poor metaboliser genotypes and to include descriptions of any new pharmacogenetic or pharmacogenomic data (obtained from advanced technologies) from exploratory or confirmatory clinical trials in regulatory submissions. An important issue will be when and how to incorporate this information into labelling and package inserts.
- It is important to maintain an open dialogue between regulatory agencies, academic researchers and pharmaceutical company scientists to explore ways that encourage and facilitate the exploratory use of pharmacogenetic/pharmacogenomic technologies and exploit the clinical value of these sciences for improving public health, without penalizing companies that choose to do so.
- One possible cause of adverse drug reactions is genetic variation in how individuals metabolise, and in some cases, transport drugs. For those drugs that are metabolised by an enzyme that is polymorphic (e.g. CYP2D6), differences in systemic exposure from a given dose should be assessed early in drug development. If these differences can be shown to be associated with a higher risk of adverse events, or failure of usually recommended doses to provide efficacy in patient subsets, this information should be included in the product label and an appropriate dose should be recommended for the subset of at-risk patients defined by genotype. Consideration would need to be given not only to the prevalence of genetic variants in the intended target population but also the clinical significance of adverse reactions, the overall risk/benefit of the drug and genotyping a large number of potential recipients of the drug.





- If genetic tests were to be used prospectively for identifying drug responders or for identifying at-risk patients, the following evidence would be necessary for regulatory approval:
  - measures of the analytical quality of the test (analytical validation)
  - data from 'functional' studies (i.e. studies that relate DNA changes to alterations in protein function and/or levels) identifying predisposing genetic/genomic factors involved with disease pathogenesis to the extent of what is known about a disease, or genetic polymorphisms that may increase the benefits or lower the risk in patients receiving drugs. These data should be supportive of the genotype-phenotype association on which the test is based and
  - information on the clinical validity and clinical utility of the test for therapeutic applications and decision making. Consideration would need to be given to the design of the pivotal clinical trials to provide sufficient information to estimate the positive and negative predictive value of any genetic test (specificity and sensitivity), and the clinical benefit to drug use with and without the use of such a test;
- There will be a need for independent replication of outcomes in the regulation of pharmacogenetic tests, i.e., to have evidence of replication of the findings of an association between the test and clinical endpoints. It will be important to establish the reliability (sensitivity, specificity etc) of the genetic test in several clinical laboratories and to assure the clinical validity of the test (both positive and negative findings). Consideration will need to be given to whether the test specified in the label of a drug product is mandatory (most likely) or optional before prescribing the drug. These considerations will take into account the rationale and level of evidence supporting the clinical utility of the test. Ideally, the regulatory authorities will approve drug-specific predictive tests recommended in package inserts at the time of approval of the drug product.
- Use of case-control pharmacogenetic and pharmacogenomic studies to explore associations between genomic biomarkers and adverse events or effectiveness with drug therapy would be considered exploratory and hypothesis generating in most cases.

## 6. Summary and conclusions

Pharmacogenetics and pharmacogenomics should be considered in all phases of drug development. These sciences have considerable potential to improve our understanding of drug safety and efficacy and to improve our development of optimal drug doses and dosing regimens.

However, with this potential in mind, the application of genetic and genomic technologies should be based on good science and applied where it has the greatest chance to improve decision making not only in drug development, but also in regulatory assessments.

Continued dialogue between academic researchers, industry scientists and regulatory agencies is needed to reduce uncertainties in the rapidly evolving fields of pharmacogenetics and pharmacogenomics. Together, they can guide strategies for exploring these technologies and utilizing data in drug development and regulatory assessment in order to optimise the benefit/risk ratios of future drugs for society.

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