Chapter 4
Regulation and public policy
Regulation and public policy

Introduction

4.1 All medicines are required to meet standards of safety and efficacy. In addition, in the UK and a number of other jurisdictions, requirements of cost-effectiveness are also applied, so that medicines offer reasonable value for money. We have already seen that the application of pharmacogenetics will have implications for the number and variety of patients who may benefit from a particular medicine. These implications raise important issues of public policy concerning equity and fairness, which we seek to address in this chapter.

4.2 We begin by considering the implications for regulators regarding the licensing of pharmacogenetic tests and medicines, both for new tests and medicines and for those medicines which have previously been withdrawn from the market. In particular, we consider the contribution that pharmacogenetics could make to improving cost-effectiveness through the reduction of wasteful prescribing, and questions of the just allocation of resources that arise as a result of the stratification of patient groups through pharmacogenetic testing.

Regulation

4.3 In the UK, the safety and efficacy of medicines is assessed by the Medicines and Healthcare Products Regulatory Agency (MHRA). The MHRA licenses new medicines for use and oversees the provision of information and warnings about products. Regulation of the quality of genetic tests is also the responsibility of the MHRA. A European directive on in vitro diagnostic medical devices (98/79/EC) was agreed in 1998 which sets out the requirements for licensing diagnostic tests. The MHRA is responsible for the implementation of this directive in the UK.

Pharmacogenetic tests

4.4 Depending on the evidence submitted to the MHRA by a pharmaceutical company that has developed a new medicine, the Agency may require the use of a pharmacogenetic test as part of the conditions of issuing a licence for its use. Notification about the need to perform the test before prescribing the medicine would then be included in the information about the medicine used by prescribers. This approach is analogous to that taken with medicines that require non-genetic tests to be carried out in order to assess the suitability of a patient for treatment or to monitor their response to the medicine. Such tests are currently used for various medicines and include tests of liver or kidney function. It is likely that pharmaceutical companies which have identified genetic variation that affects response to a new medicine will include this information in their application and will support its inclusion in the licence. There will be legal incentives for this approach, as including the information in the product licence will discharge a company’s legal obligation to make prescribers and patients aware of relevant information about safety and efficacy. Furthermore, regulators may require the disclosure of such information. Companies could advise prior testing for all potential patients for whom the medicine is intended, or for specific groups considered to be at risk.
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due to factors such as sex, age or ethnicity. If it would be unsafe to prescribe a medicine in the absence of a test, or if the test provides very strong predictions of efficacy, it will be in the manufacturer’s interest to ensure that the test is available, either from the manufacturer or from a diagnostic company.

4.5 In the case of medicines that have already been licensed, pharmacogenetic tests that are subsequently developed will not be part of the licence conditions. However, the MHRA reviews the conditions of licences once every five years, and could decide to include a pharmacogenetic test as part of a review, or at another time. This possibility is illustrated by the example of a pharmacogenetic test that predicts response to the medicine 6-mercaptopurine for children with acute lymphoblastic leukaemia (ALL). This rare childhood cancer is commonly treated with 6-mercaptopurine, which is metabolised by the enzyme thiopurine methyltransferase (TPMT). Around 10% of Caucasians have genetic variants that lead to reduced levels of the enzyme. In these patients, 6-mercaptopurine can build up in the bloodstream and lead to serious toxicity. Patients deficient in TPMT can be identified through the use of a pharmacogenetic test and their dosage of the medicine reduced accordingly. This pharmacogenetic test is marketed and used, although it took about 20 years for the discovery of this phenomenon to be incorporated into clinical practice, and in the UK, most physicians only use the test once a patient has shown signs of an adverse reaction. In the US, the FDA has recently announced that it is considering recommending the use of the pharmacogenetic test to guide dosing.

4.6 It is most important that pharmacogenetic tests are developed which are of high quality and able to identify the genetic variations in question accurately. The MHRA is responsible for ensuring that only pharmacogenetic tests of high quality are approved for use. We recommend that the European Medicines Evaluation Agency (EMEA) and the Food and Drug Administration (FDA) provide guidance for applicants as to the circumstances in which pharmacogenetic tests will be incorporated into the licence conditions of a medicine. Relevant factors will include the reliability of the test, the level of information it provides, and the frequency and magnitude of the effect it predicts, whether an adverse reaction or a poor likelihood of response.

Withdrawn medicines

4.7 The most common reason for medicines to be withdrawn from the market once they have been licensed is the subsequent occurrence in patients of serious adverse reactions, which were either unsuspected at the time of marketing authorisation or occur more frequently than was expected at the time of the grant of marketing authorisation. If at least some

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4 It should be noted, however, that the TPMT test, while providing high specificity (i.e. a patient who tests positive is definitely at high risk) has quite limited sensitivity (i.e. a significant number of patients who test negative will still have the adverse reaction). Thus, the pharmacogenetic test does not remove the need to monitor patients closely when they receive the medicine.


7 It is comparatively rare for medicines to be withdrawn from the market once they have been licensed. Between 1998 and 2002, the Medicines Control Agency awarded over 200 new licences, of which 12 were subsequently withdrawn because of safety concerns (National Audit Office (2003) Safety, quality, efficacy: regulating medicines in the UK (Norwich: The Stationery Office, HC 505)).
adverse reactions can be explained by genetic variation, pharmacogenetic analysis might enable medicines that have previously been licensed but then withdrawn to be reinstated, by allowing the prior identification of individuals likely to suffer from adverse reactions. It may also be the case that compounds already rejected during the process of development could be reconsidered as potential treatments for genetically-defined groups of patients.

4.8 It has been suggested that pharmacogenetics will be of value in retrieving withdrawn medicines.⁸ An example that has been cited is the medicine Lotronex, used for the treatment of irritable bowel syndrome. This medicine was approved in 2000 in the US, but was subsequently withdrawn by the manufacturer, GlaxoSmithKline (GSK) when it became apparent that some patients experienced adverse reactions. The FDA and GSK are now working to re-examine the medicine, and one element of this process includes the pharmacogenetic analysis of samples from the patients who have been prescribed the medicine.⁹ However, it is not clear at this stage whether this will enable the prediction of patients who are likely to be adversely affected. It is worth noting in this context that regulatory bodies such as the FDA have been exploring methods of enhancing post-market surveillance by pharmaceutical companies.

4.9 There are various reasons why re-licensing a medicine that has previously been withdrawn may not be possible. First, although regulatory requirements for re-licensing a medicine are not formally set at a higher level than those for the original licence, a convincing case for re-licensing must be made. Secondly, pharmaceutical companies may not have stored genetic information from patients either during clinical trials or subsequently, in which case it would be very difficult to identify relevant pharmacogenetic variants, as new samples could not be collected once the medicine has been withdrawn. Even if some data are stored, they may not be sufficient to obtain a statistically significant result. Thirdly, if alternative treatments are available which do not require pharmacogenetic tests, there will be less reason to invest in producing a medicine which also requires a test, since this is unlikely to be competitive. Fourthly, unless medicines are protected by patents, there will be little incentive to invest in further research. Finally, negative attitudes towards the medicine may have become established, which could be difficult to surmount.

4.10 We conclude that medicines that are found to cause adverse reactions are unlikely to be re-licensed, even if pharmacogenetic analysis is subsequently carried out which could lead to the development of a useful test. An exception might arise in cases where there is no alternative treatment available. The low likelihood of pharmacogenetic analysis leading to the re-licensing of medicines is unfortunate, because there would be obvious benefits in reintroducing a medicine that is effective in one group of patients while eliminating the threat it poses to another group.

The allocation of resources

4.11 Both public and private providers of healthcare operate on limited budgets. In addition to the traditional requirements of quality, efficacy and safety for the regulatory approval of new medicines, public policy in many countries is developing the requirement to assess medicines for their cost-effectiveness. That is to say, the question is not simply whether the medicine has its intended effects and is safe when it is administered, but also whether the

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cost of the medicine represents good value for money, given the health benefits that it is expected to produce. In this section, we consider the implications of pharmacogenetics for providers of healthcare. We focus primarily on public provision, since in the UK, most medicines are provided by the National Health Service (NHS).

4.12 Cost-effectiveness is a measure of the ratio between what a medicine costs to deliver and what benefits it is intended to produce. In principle, it can be assessed in a number of ways. In the simplest imaginable case, the assessment rests upon the comparison of two medicines with equal effectiveness but which cost different amounts, as is alleged to be the case between some branded medicines and their generic equivalents. Clearly, in this sort of case, the more cost-effective medicine would be the cheaper of the two. However, comparisons are rarely so simple, and the difference in the cost of two medicines is likely to be matched by differences in efficacy of treatment and the probability of adverse reactions. Given these differences, an approach is needed which sets the cost of the medicine against some measure of their benefits in order to assess which is the more cost-effective of the two.

4.13 Health economists have developed a number of ways of assessing cost-effectiveness in these sorts of cases, all of which depend upon being able to place a numerical value upon the benefits that a medicine produces. One approach compares the costs and benefits of a healthcare intervention, representing the benefits in non-monetary terms such as life years gained, or number of days free of pain. This approach can be extended to a cost-utility analysis, which seeks to place a value on the benefits that recipients of a medicine derive based upon the patients’ own evaluation of alternative outcomes. One particularly influential variant of this approach uses the notion of ‘quality adjusted life years’, or QALYs.

4.14 A QALY assessment can take many forms. However, it can be illustrated as follows. Respondents to a survey may be asked their relative evaluations of health outcomes associated with different levels of distress or disability. A fully healthy individual will be one having a year of life with no distress or disability. Varying combinations of distress or disability will reduce the value of that life year, and the task of researchers is to scale those combinations relative to the alternative of full health. For example, a state in which someone’s choice of work is severely limited will be matched against a state in which there is only slight impairment of work ability but there is associated pain. The scales derived from these comparisons are then used to adjust the value of the estimate of life years gained. A QALY is the arithmetic product of the number of life years gained by an intervention and the quality of life during these years. In effect, the value of an added year is adjusted to take into account deterioration in the quality of life.

4.15 The use of QALYs has been criticised on a number of grounds. They are difficult to calculate in a way that carries inter-subjective conviction. The amount of research into measuring QALYs in relation to particular conditions varies: in the case of subgroups of diseases that are identified as a result of pharmacogenetics this could be especially problematic. The difficulties of producing a single QALY estimate for a disease suffered by a number of people are considerable. Despite these problems, QALY estimates do address the important issue of estimating not simply length of extended life but also the quality of life that is experienced, and it is for this reason that they have been taken up by policy-makers. Provided that they are used as an aid to judgement rather than a substitute for judgement, they can play a constructive role in decision-making.

4.16 Various countries have developed systems for assessing whether medicines should be provided as part of a public healthcare system. In Australia, the Pharmaceutical Benefits Advisory Committee is an independent statutory body that advises the Ministry of Health...
and Aged Care and the Pharmaceutical Benefits Pricing Authority about which medicines should be made available through the public healthcare system. No new medicine may be made available unless the Committee has so recommended. The Committee is required to consider the effectiveness and cost of a medicine compared to alternative therapies. In Canada, the Canadian Coordinating Office for Health Technology Assessment is a national, non-profit organisation that reviews research on medical technologies such as devices and medicines, focusing on evaluations of clinical effectiveness and cost-effectiveness, to aid decision-making by the ministries of health, Health Canada, hospitals and health practitioners. In New Zealand, PHARMAC (Pharmaceutical Management Agency), a government body, is responsible for national pharmaceutical policy. Decisions on the subsidisation of medicines are made by PHARMAC with input from independent medical experts on the Pharmacology and Therapeutics Advisory Committee and its specialist sub-committees, and the staff of PHARMAC.

4.17 In England and Wales the responsibility for assessing cost-effectiveness falls to the National Institute for Clinical Excellence (NICE). In Scotland, NHS Quality Improvement Scotland has invariably accepted guidance from NICE. There is currently no analogous body in Northern Ireland, although guidance produced by NICE may be adopted. For the purposes of this section, we will focus on NICE, as the organisation covering the largest proportion of the population of the UK. The remit of NICE includes the appraisal of technologies and the production of clinical guidelines. In terms of technology appraisal, NICE assesses the evidence base for clinical and cost-effectiveness of new and existing health technologies such as medicines, diagnostic tests, clinical devices and procedures. The Institute receives requests for examination of particular health technologies from the Department of Health (DoH) and the Welsh Assembly Government and undertakes a detailed process of appraisal over a period of approximately 12 months. As part of the appraisal process NICE invites contributions from relevant stakeholders and considers, in particular, five areas:

- **Disease background**: epidemiology, aetiology, pathology and prognosis.
- **Description of the technology**: mode of action, indication, projected cost of treating the targeted disease.
- **Clinical effectiveness**: evidence of the quality of the technology, benefits and disadvantages over competing products, including adverse effects.
- **Cost-effectiveness**: the balance between benefits and cost, usually expressed as cost per QALY or cost per life year gained.
- **Wider implications for the NHS**: health gains expected from the intervention, likely budgetary impact, required changes in work pattern or reconfiguration of services, education and training issues.

After further consultation, the outcome of the appraisal system falls in three broad categories:

- The technology is recommended for routine use in the NHS, for all licensed indications, for specific indications, or for specific subgroups only.
- The technology is recommended only for use in appropriate clinical trials.
- The technology is not recommended for use in the NHS for any group of patients for specified reasons relating to lack of clinical or cost-effectiveness.

NICE does not operate a ‘threshold’ cost per QALY or life year gained. Instead, the probability that a technology will be recommended for routine or selective use in the NHS
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decreases as cost-effectiveness decreases. While NICE has been more reluctant to recommend treatments with a cost per QALY of over £30,000, it has endorsed one treatment at £49,000 per QALY.10

4.18 It is important to underline the fact that NICE does not operate by imposing thresholds. A simple application of a threshold would be tantamount to saying that cost-effectiveness was the only principle of allocation that is relevant to the allocation of resources and that the sole aim of public policy should be to maximise the amount of benefit, measured in terms of QALYs, for the population as a whole, for any given level of expenditure. As has been pointed out, however, such an approach risks ignoring considerations of justice or equity.11 On this view, it is not the total increase in QALYs which is important, but the fair distribution of that benefit among the members of a population. Such considerations need to be set alongside those of cost-effectiveness.

4.19 The difficulty of relying solely on the principle of cost-effectiveness is that it may lead to those suffering from rare conditions being overlooked in the allocation of resources because their numbers are not large enough to count against the more prevalent conditions. Yet, in liberal democratic societies, a widespread sense of justice includes the belief that everyone is owed a certain minimum entitlement, no matter how small the minority to which they might belong. These entitlements include access to health services relevant to the illnesses from which they are suffering. Hence, it may well be right to allocate resources to the treatment of those suffering from a rare condition, even if this means that these resources are less productive of overall benefit.

4.20 In recognising the case for such entitlements, we should not dispense with information about the relative cost-effectiveness of different medicines. However, the recognition of arguments about equity does affect our interpretation of such data. In particular, we should not assume that estimates of cost-effectiveness carry the implication that the goal of public policy should be to maximise the gain in health of the population. Instead, we should take estimates of cost-effectiveness as information to aid in a process of decision-making which comprises substantive considerations of justice and overall social well-being.

4.21 The issue is important because by and large the decisions of bodies such as NICE have considerable influence. In the UK, despite there being controversy over a few appraisals of medicines, of which the case of beta interferon was the most significant, the recommendations of NICE have not only imposed a fair and rational framework on decision making, but have generally received wide acceptance.12 If the advent of pharmacogenetics looks as though it will disrupt this legitimacy, then care needs to be taken as to how principles of allocation can be developed. We endorse the approach taken by the National Institute of Clinical Excellence (NICE) of reviewing cases on an individual basis, not applying thresholds, and incorporating considerations of both equity and cost-effectiveness.

4.22 How will pharmacogenetics affect decisions on the allocation of resources, and what are the relevant principles to be borne in mind? We noted in paragraph 3.15 that the aggregate effect of the development of pharmacogenetics in terms of the total cost of medicines for

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a healthcare system is difficult to assess. There are competing forces at work in this area. On the one hand, pharmacogenetics provides the ability to target the development of medicines more precisely, possibly leading to lower development costs. Moreover, the ability to identify those patients most likely to benefit from a particular pharmaceutical product means that those investing in medicines research should have greater certainty of return. On the other hand, pharmacogenetics threatens to fragment the market, reducing the economies of scale that have been associated with the profitable ‘blockbuster’ products of the past. How these competing forces will balance out is impossible to say at the present time. The implication is that it is not clear whether the search for cost-effective medicines will be made easier through an overall lowering of the costs of development or harder through an overall increase in the cost of supplying medicines. However, whichever of these outcomes prevails, the search for cost-effective allocation will take place within an overall constraint on costs.

4.23 In this context, there are likely to be at least three ways in which the application of pharmacogenetics will affect the search for a fair and reasonable way of obtaining value for money in the use of pharmaceuticals: from the greater ability to avoid adverse reactions; from the greater ability to identify potential response rates by different classes of patients to any medicine; and from the possibility of identifying additional groups of patients who can be thought of as having an ‘orphan’ condition. We consider the question of adverse reactions first, before turning to the issues raised by the stratification of patient populations.

The prediction of adverse reactions

4.24 If we consider the application of pharmacogenetics in the identification of adverse reactions, then the effects on cost-effectiveness should in general be wholly positive. By definition, a group of patients suffering an adverse reaction is experiencing a loss of benefit. If it is possible in advance to identify the patients for whom the medicine should not be prescribed, then not only are the patients protected, but the cost of prescription is avoided for a group for whom the medicine would not be of benefit in any case.

4.25 Pharmacogenetics promises a situation in which there is less trial-and-error prescribing. For example, we heard evidence from the charity Rethink about the difficulties that patients suffering from schizophrenia experience, before the right treatment regime is found for their condition. If the difficulties arising from this trial-and-error prescribing could be avoided, then there would be an improvement in the quality of treatment. Such an improvement in quality is an enhancement of benefit for which in economic terms there ought to be a greater willingness to pay, and this ought to be reflected in economic and ethical assessments.

4.26 A special case would arise if a pharmacogenetic test reveals that a group of patients are likely to suffer an adverse reaction, but it is still to the overall benefit of those patients to continue taking the medicine because the benefits outweigh the disadvantages. In this situation all the pharmacogenetic test has done is to identify which type of patients will be adversely affected without there being any corresponding improvement in cost-effectiveness. However, this is no different from the situation that would have existed without the pharmacogenetic test. The best that one can hope for in this context is that the information revealed in the pharmacogenetic research proves useful for developing better medicines for the adversely affected subgroup.
Stratification and the allocation of resources

4.27 We observed in paragraphs 2.6 – 2.10 that the application of pharmacogenetics could lead to the stratification of patients into different groups according to their response to medicines, or according to the features of their disease. The first approach is, in many cases, already current practice, although not based on genetic data: it would mean that a doctor would choose between a variety of medications, or, less commonly, between a variety of dosages. The second might entail that a variety of specialised medicines will be recognised as effective treatment of similar symptoms or conditions in different groups of patients, according to their genotypes. However, as we observed in paragraph 2.5, it is impractical to suggest that truly personalised medicines will be developed for each individual patient.

4.28 Whatever the likely consequences in terms of the match between the individual patients and medicine might be, it is clear that distinguishing patients into subgroups raises serious ethical problems. In order to appreciate these problems, consider a highly simplified example. Suppose that there is a condition that has been treated by a particular medicine. Genetic tests now show that potential patients can be divided into two groups of equal size: Group A, who have an 80% chance of responding positively to the medicine and Group B, who have a 15% chance of responding positively. If £10,000 per patient is spent on each group, then in Group A the overall cost per QALY might be £12,500 and in Group B over £66,000 per QALY. We noted earlier that the probability of a body such as NICE recommending a technology decreases as cost-effectiveness decreases. In this situation, therefore, it is likely that such an authority might reject the medicine for patients falling into Group B whilst recommending use in those who fell into Group A. Is this fair?

4.29 One reason why one might think that it is fair to advise in such a way is that the situation is no different, from an ethical point of view, to one in which there were two groups of patients with disease conditions which could be treated by different medicines, but where one medicine was much more expensive than the other. This reflects the fact that low cost-effectiveness can arise in two ways. Health gain may be low in a group of patients or overall costs may be high. Either way, it might be argued, in so far as considerations of cost-effectiveness have any independent weight, we may find ourselves in a situation in which the medicine is recommended for one group but not the other. All that we have done with pharmacogenetic information is to acquire the ability to predict in advance which groups of patients are likely to be high or low responders. Prior to the advent of any pharmacogenetic test it would still have been possible to assess effectiveness biochemically or pharmacologically and cease treatment for those not responding. In other words, the pharmacogenetic technology does not change the situation in respect of its underlying ethical dimensions. If it was ethical to apply the arguments about cost-effectiveness before the pharmacogenetic intervention, it should be so afterwards.

4.30 Of course, considerations of cost-effectiveness are not the only considerations that have weight. As we have already noted (paragraph 4.19) concerns of justice and equity will mean that sometimes it will be right to allocate resources to conditions that in other circumstances might be considered to be cost ineffective. However, at some point, considerations of cost-effectiveness will imply that resources will not be allocated to patients who are expensive to treat where the estimate of the cost of treatment will be dependent on a pharmacogenetic test. In practice, decisions regarding cost-effectiveness are likely to be more complex than the simplified example in paragraph 4.28 suggests.

4.31 It might seem that it is artificial to be drawing distinctions between groups of patients. However, although drawing the line is in some ways artificial, this does not mean that it is unfair. Where there is a valuable social purpose to be served and some form of restriction
needs to be put in place, then given the nature of human attributes this will almost
certainly mean drawing clear lines, or setting thresholds, in continuous distributions. So
long as the distinction is not made so as to produce some form of favouritism, then one
can justify the allocation.

4.32 We conclude therefore that although the partitioning of patients into genetically distinct
subgroups is going to make decisions on the evaluation of medicines more difficult, with
finer lines to be drawn, we do not think that there are new ethical issues that arise from
this fact alone. However, it is important that such evaluation is undertaken in a context in
which a range of relevant considerations is allowed to influence the decision, and this point
reinforces our earlier endorsement of the rejection by NICE of a simple threshold test
(paragraph 4.21).

**Stratification and the development of new medicines**

4.33 Stratification is relevant to the development of medicines targeted at genetic features of
diseases, such as subgroups of cancers. But it may also arise in the development of other
medicines, especially if relatively cheap and reliable pharmacogenetic tests can be
developed which are good predictors of safety or efficacy. What might be the implications
of such stratification for patients and for pharmaceutical companies? From an economic
perspective, it could be argued that the identification of smaller, more narrowly defined
groups of patients for whom a medicine is appropriate will have a negative effect on
profitability. So-called ‘blockbuster’ medicines generate substantial revenue because they
are sold to a very large patient population identified as having the symptoms or condition
in question.\(^\text{13}\) If such a population is stratified, a company wishing to reach the same total
patient group that had previously been prescribed a single medicine would have to meet
the additional expense of developing a number of medicines. However, reductions in the
size of markets as a result of stratification may be offset by the ability of companies to
develop targeted medicines that may otherwise have been rejected during development.
This could occur by producing pharmacogenetic tests to identify and exclude those at risk
of adverse reactions, or by defining a specific group of patients in whom the medicine will
be particularly effective.

4.34 It has been suggested that if stratification means that medicines are considerably more
effective in defined patient groups, they may command a premium price, making their
development profitable despite the smaller market.\(^\text{14}\) This however presumes that
providers of healthcare, whether public or private, are able or willing to meet such higher
costs. It is also possible that the application of pharmacogenetics could have the opposite
effect. Rather than distinguishing small subgroups of patients, the developers of new
medicines might seek instead to maximise the number of patients who would benefit from
a medicine by using pharmacogenetic information to identify medicines most suited to
large groups of patients.

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\(^{13}\) In recent years, most pharmaceutical companies have focused on the commercialisation of a relatively small number of
medicines, each of which has an exceptionally promising market potential. In practice, a minority of the products of a
company generate most of its revenue. In 1999, 18 pharmaceutical companies produced at least one medicine which had
global sales of at least US$750 million annually, and six had three or more such products (Mercer Management Consulting
(2001) *Where are the next profit zones in pharmaceuticals?* (Boston: Mercer Management Consulting)).

\(^{14}\) See for example Peakman T and Arlington S (2001) *Putting the Code to Work: The Promise of Pharmacogenetics and
Pharmacogenomics*. (Price Waterhouse Coopers). Eisenberg suggests that ‘patients should be willing to pay more for drugs that
have been preselected to work well for them than they now pay for drugs that might have no benefits or toxic side effects’.
4.35 It is not clear whether research in pharmacogenetics will produce data that are sufficiently predictive to be used in clinical practice, and therefore lead to increased stratification of patients and of diseases. There are recent examples where new medicines have been developed and licensed despite, or perhaps as a result of stratification, such as Herceptin (Box 2.3: Case study 2). It remains a possibility, however, that if a market segments into a number of parts, each may be too small to provide an incentive for research and development. Estimates about the degree to which it may be in the interest of pharmaceutical companies to develop medicines for smaller groups of patients are currently highly speculative, but the possibility of unprofitable markets emerging as a result of pharmacogenetics cannot be ruled out. If this possibility were realised, it could be argued that incentives should be put in place to promote the development of medicines for patients who might otherwise be neglected in virtue of the rarity of their condition, or their unresponsiveness to existing medicines. In such cases, what kinds of incentive might be needed to encourage the development of new medicines?

4.36 Formal regulatory incentives to develop medicines currently exist in the case of rare diseases. These diseases are called ‘orphan diseases’ and the medicines that treat them are called ‘orphan medicines’, because they are unlikely to generate sufficient economic revenue to the pharmaceutical industry to be developed without subsidy or some other public policy measure. The basic principle behind this willingness to provide special incentives for the development of orphan medicines can be simply stated. The legal and economic conditions under which medicines are developed, and in particular the terms under which patents are awarded, will determine the rate of return for an investment in the development of a medicine. However, the operation of those terms can lead to a situation in which there is no economic incentive to develop the medicine, even though the benefits of the development, in terms of the number of patients treated, would, in the long run, outweigh the costs. Hence, the question is whether the benefits could be achieved by enabling companies to realise the potential returns by altering the terms under which they can bring a product to market.\footnote{Rai AK (2002) Pharmacogenetic Interventions, Orphan Drugs, and Distributive Justice: The Role of Cost–Benefit Analysis, Social Philosophy and Policy 19: 246-70.}

4.37 In such cases, what kinds of incentive might be needed to encourage the development of new medicines? In a number of countries, specific legislation has been enacted to provide incentives to industry to undertake research and development for orphan diseases (see Box 4.1). Definitions of orphan medicines specify the level of incidence of a disease below which treatments will be eligible for orphan medicine status (see Box 4.2). In the US, the status of orphan medicine can also be granted when there is a reasonable expectation that the cost of developing the medicine will not otherwise be recouped.\footnote{Orphan Drug Act 1994, 21 USC §360ee(b)(2).} It should be noted that the criteria in Box 4.2 depend on the incidence of the disease on a national level. Companies who develop medicines, however, operate on a global level. If numbers of patients for a prospective orphan medicine are aggregated across countries, the number of potential recipients clearly increases, notwithstanding the additional costs of different regulatory and marketing requirements in each country. It could therefore be argued that incentives for pharmaceutical companies might not be required if a global perspective is taken. Additionally, if a medicine is effective in prolonging the lives of patients who would otherwise have died, the patient population will increase over time. (This possibility is accounted for in the European system, which allows for the status of orphan medicine to be reassessed and withdrawn if the criteria are no longer met.)
Box 4.1: **Orphan medicine regulation in Europe and the US**

General features of regulation relating to orphan medicines are that governments offer patent protection beyond the normal periods, as well as tax credits and incentives for research. The relevant regulation in the European Union is the *European Regulation on Orphan Medicinal Products* (2000). In the US, incentives for the development of orphan medicines are provided for by the Orphan Drug Act (1983) (ODA). The features of both sets of regulation are set out below.

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<td></td>
<td>Developed by individual member states</td>
<td>Up to 50% of clinical trial costs may be credited against tax</td>
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<th><strong>Designation criteria</strong></th>
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<td>Based on prevalence or on the likelihood of profitability</td>
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<td>Requires that ‘no other method’ exist (unless there is a significant additional benefit to patients)</td>
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<th><strong>Market exclusivity</strong></th>
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<td>Given for 10 years but reassessed after 6 years and withdrawn if criteria are no longer met, for example, if the prevalence of the disease has increased, or if another product has been developed which is safer and more effective</td>
<td>Given for 7 years (no reassessment).</td>
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<td>European Commission, European Medicines Evaluation Agency (EMEA), member states of the European Union</td>
<td>Food and Drug Administration (Office of Orphan Products Development)</td>
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<td>Assistance with developing research protocols</td>
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<td>Grants to encourage research into rare diseases</td>
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<td>Fee exemptions</td>
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<td>Waiver of certain application fees</td>
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<td>Centralised regulatory procedures</td>
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*European Regulation on Orphan Medicinal Products* (2000).
4.38 It is not clear how orphan medicine legislation will be applied to pharmacogenetic medicines. The medicine Herceptin (see Box 2.3: Case study 2) was not granted the status of orphan medicine in the US. It is estimated that of the more than 1.5 million women in the US who have been diagnosed with breast cancer, approximately 165,000 have metastatic breast cancer. Up to 30% of these 165,000 women could benefit from Herceptin. Since the criterion for orphan disease status in the US is that 200,000 or fewer patients are affected, both metastatic breast cancer and the subset of metastatic breast cancers that would respond to Herceptin might seem eligible. However, the FDA took the view that the patient population for Herceptin comprises people with breast cancer, who number considerably more than 200,000. The FDA was apparently not inclined to define a subset of patients as having a distinct condition based on the genetic characteristics of their tumours. (Interestingly, Herceptin was granted the status of orphan medicine for the subset of pancreatic cancers that over-express HER2.) Medicines are most commonly denied orphan medicine status because of disagreements over how target populations are defined. Although rejections might, in many cases, be justified, to prevent pharmaceutical companies from dividing markets in a creative way, these cases nevertheless suggest that the seemingly academic issue of reclassification of disease through pharmacogenetic analysis might have significant implications for regulatory frameworks. The potential need for regulatory agencies to reconsider definitions of orphan medicine in the light of advances in pharmacogenetics was highlighted by numerous respondents to our consultation, including the Association of British Pharmaceutical Industries, Pfizer, Indiana University Center for Bioethics, and the Pharmacogenetics Evaluation Policy Project.

4.39 Although it might seem plausible to argue that incentives and forms of subsidy should be expanded as much as possible to encourage the development of appropriate medicines for groups of patients no matter how rare the incidence of their condition might be, such arguments need to be more nuanced. For example, subsidies allocated under such regulations may have an impact on the pharmaceutical market, as the reduction of risk for pharmaceutical companies indirectly increases the rate of return. Further, it is likely that the provision of public subsidies for medicines to treat particular rare conditions will be influenced by the respective lobbying power of particular patient groups. One respondent to our public consultation observed that orphan medicine legislation involves ‘subsidy, directly or indirectly, of the pharmaceutical industry by the public purse, except where the

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**Box 4.2: Criteria for granting the status of orphan medicine**

<table>
<thead>
<tr>
<th>Europe</th>
<th>US</th>
<th>Japan</th>
<th>Australia</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 in 10,000 (approx. 190,000 patients)</td>
<td>7.5 in 10,000 (approx. 200,000 patients)</td>
<td>7 in 10,000 (approx. 100,000 patients)</td>
<td>1 in 10,000 (approx. 2,000 patients)</td>
</tr>
</tbody>
</table>

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cost of medicines is borne entirely by individual patients’.20 Hence policies to provide further incentives through public subsidy require careful examination.

4.40 In conclusion, pharmacogenetics is likely to influence the development of new medicines by affecting the conduct of clinical trials and perhaps by redefining groups of patients. Some potentially valuable new medicines may not be developed if, as a result of genetic stratification, the number of patients who would benefit is too small to be profitable. However, stratification may also enable some medicines to be developed that would otherwise have failed because the subgroup in which the medicine is effective can now be distinguished. It is currently uncertain which of these trends is likely to prevail. We therefore recommend that agencies responsible for the licensing of new medicines pay attention to the possible negative effects of stratification. If pharmacogenetic stratification does provide an economic disincentive for those developing new medicines, consideration should be given to preparing guidance notes that encourage applications to use existing orphan medicine legislation, or any other policy instrument with equivalent effect, to provide incentives for development. We further recommend that if orphan medicine legislation is to be applied, consideration is given by the International Conference on Harmonisation to a global approach to orphan medicine legislation. This should include reconsideration of the definition of an orphan medicine, with particular reference to the implications of genetic stratification of both patients and diseases.

Pharmacogenetics and racial groups

4.41 A particular case of the stratification of patient populations is stratification based on racial or ethnic groupings. Race and ethnicity cannot be given precise biological or genetic definitions. There is considerable genetic variation within racial and ethnic groups, whether defined by place of birth, self-identification or other criteria, as well as between them. Nonetheless, some genetic variants are more common in some racial or ethnic groups than in others. Some early research in pharmacogenetics, before genetic markers were available, hinged on the interpretation of differences that were observed between various racial or ethnic groups. An example of a variant that has different frequencies in different population groups is the CYP2D6 genetic variant discussed in Box 2.2: Case study 1. This variant is present in approximately 7% of Caucasians, but only 1% of Chinese people. Similarly, one variant of the TPMT gene, TPMT*3A, which affects response to a medicine used in the treatment of childhood leukaemia (paragraph 4.5), is present in 4% of Caucasians but is not found in Chinese or Japanese populations.21

4.42 The fact that some genetic variants are more or less likely to be found within particular groups has implications for the design of clinical trials and for the development of medicines. In the case of research and development, it means that comparisons of trials conducted in different countries, or statements about efficacy based on evidence in one particular population, may not be valid in other, genetically different populations, or may only be valid if a different prevalence in relevant genetic variants has been taken into account. This problem of comparability between different groups has always been present and has been addressed by various bodies.22 Pharmacogenetic testing may simply make it

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22 ICH Topic E5 – Note for Guidance on Ethnic Factors in the Acceptability of Foreign Clinical Data (CPMP/ICH/289/95)
more explicit. Some pharmacogenetic research examines genetic variants which are not themselves causally related to the effect being studied, but which are associated with the genetic variation that is responsible for the effect. In such cases, the problem of translating research results across populations becomes more acute. It is possible that the non-functional genetic variation which is tested for may not co-occur with the functional genetic variation in other groups.

4.43 It is important that applications seeking approval for a medicine or a pharmacogenetic test are supported by data collected in the relevant population. This will be particularly important if pharmacogenetic research is conducted in groups that are genetically relatively homogeneous. In the US, the FDA requires that analyses of data regarding effectiveness and safety for important demographic subgroups, including race, be included in applications for the approval of new medicines. This information must be included on product labels. A similar requirement exists in the UK. However, there is no parallel requirement for genetic tests. We recommend that bodies giving approval for the clinical use of pharmacogenetic tests require these to specify the population groups in which the tests have been validated, and to issue warnings where there is evidence that such tests may not be usefully predictive of response to medicines in other population groups.

4.44 Acknowledging that genetic variation between population groups should be taken into account in the design of medical research should not be taken to imply that there are sharp lines that can be drawn between groups on the basis of genetic information which coincide directly with racial categories. Given the variation within racial groups, and the myriad ways in which these are defined, there has been considerable debate about whether racial categorisations are meaningful in the field of genetics. Outside genetics, such categories are being used in the development and marketing of medicines. In 2001, research was published which showed that a treatment for heart failure called enalapril was less effective in black patients than in white patients. In 2002, the FDA approved a clinical trial of a new medicine for heart disease that would only recruit black participants. This trend is likely to be magnified by the increased application of pharmacogenetics.

4.45 In those countries where medicines are advertised directly to consumers, there is a serious risk that medicines could be marketed to particular racial groups in a misleading manner, giving the impression that all members of that group would be likely to benefit, or that the

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medicine was more effective than other, non-racially defined medicines. More generally, such developments may reinforce tendencies to view race as a biologically-defined phenomenon. We recommend that those involved in pharmacogenetic research and the development of new medicines should be sensitive to the potential for misunderstanding and prejudice arising from racial stereotyping. We recommend further that regulatory bodies exercise careful scrutiny over claims as to racial specificity in the marketing of pharmacogenetic tests and medicines.

4.46 Denying treatment to a particular racial group, using race as a proxy for a genetic profile, would be problematic, since not every member of the group could be expected to have the genetic variant in question. It is possible that health professionals would be tempted to use race as a proxy in determining treatment, if the pharmacogenetic test that would discriminate more accurately was not readily available. Since clear-cut divisions between racial or ethnic groups are highly unlikely, we take the view that membership of a particular racial group cannot be used as a substitute for a pharmacogenetic test, even if it is the case that the genetic variant being tested for is known to be more or less prevalent in particular groups.

4.47 A further potential problem arises if stratification results in the members of some ethnic groups finding that they are denied access to medicines when others of different ethnic groups, but suffering the same condition, are allowed access. This would be a particular cause for concern if the group being denied treatment was already socially and medically disadvantaged. At the present stage of development, we cannot say how great a problem this is likely to be. However, it is something that should be monitored. We recommend that those responsible for monitoring the relative access of different ethnic groups to treatment in the National Health Service establish procedures for assessing whether problems emerge arising from the development and application of pharmacogenetics.