Realising the Potential of Genomic Medicine

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Acknowledgements

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Executive summary

Chapter 1. Introduction: the promise of genetics, genomics and molecular medicine

1.1 The sequencing of the human genome has sparked great interest in what many have called 'genomic medicine'. Advocates claim that knowledge of the genome will usher in a new era in medicine, which will focus on prevention rather than cure and personalised treatment based on new and more powerful therapies. This prospect is often couched in terms of a 'revolutionary' change, underscoring the idea that the genomic era will bring about a different sort of medicine. In terms of specific technologies, genomic medicine falls under three broad headings:

    a. The development of new gene-based diagnostics for common conditions
    b. The introduction of pharmacogenetics or so called 'personalised medicine'
    c. The creation of novel biological therapies

1.2 As well as the anticipated health benefits, genomics is also being increasingly seen as a key element of the new knowledge based economy, with analysts predicting the creation of thousands of new jobs in the biotechnology sector across Europe. If these hopes are realised, the rise of genomic medicine is likely to have major implications for the future development of healthcare and the work of all professional groups in the health service. It is therefore important that a careful assessment is made of the current development and medium term prospects for this group of technologies in order to help guide policy and inform the work of professional bodies such as the Royal Pharmaceutical Society.

1.3 This report has been commissioned to inform the development of the next phase of the Pharmacy Practice Research Trust's *Medicines and People* programme, which is designed to deliver the knowledge needed to understand and develop polices relating to the complex process of: *Getting the right medicine to the right person at the right time in a manner that meets the needs and expectations of the individual who will take it.*

1.4 This report therefore aims to:

- Briefly describe the main scientific and technical advances in the area of genomic medicine
- Assess the prospects for the short and medium term development of these technologies, their potential benefits and possible social and ethical implications
- Identify the main changes in policy, practice and the organisation of healthcare that might be needed to accompany their introduction
- Identify key areas of research that would inform the development of policy relating to the implementation and uptake of the scientific and technical advances in genomic medicine, focusing on the main themes in the Medicines and People programme

Chapter 2. New molecular diagnostics: genetic tests and protein biomarkers

2.1 Genetic testing generally refers to the direct testing of an individual's DNA where there is some evidence of disease. This is distinct from genetic screening, which involves testing families or populations where there is no prior evidence of disease. There are a number of different forms of genetic testing, including confirmatory diagnosis; carrier testing; prenatal/neonatal screening; predictive and susceptibility testing; and pharmacogenetic testing.

2.2 The bulk of genetic testing in the NHS is performed in the 20 Regional Genetics Centres, each serving a population of 2-6 million people. These centres offer clinical diagnosis, laboratory testing and counselling services for individuals and their families. Existing services provide low volume testing and counselling to small, widely dispersed patient groups. However, increased workload, caused partly by the availability of the predictive BRCA 1 & 2 tests for breast cancer, has placed a strain on existing services. In response to the possibility of a future expansion in testing, over £80 million has been invested to strengthen genetic testing services since 2001.

2.3 In general, new genetic tests have come into clinical use in the NHS through the research activities of particular centres rather than in a co-ordinated or uniform fashion, and access to many tests has depended on local expertise and available funding. Part of the rationale for the recent creation of the UK national Genetic Testing Network (UK GTN) is to ensure greater standardisation of services.

2.4 Historically, it has been cytogenetic methods of testing that have made up the vast majority of services. Subsequently, molecular genetic testing was developed in the mid 1980s in research laboratories where those disease genes mainly involved in rare single gene (monogenic) conditions were identified. The main area where monogenic genetic testing is on the increase is in newborn screening programmes. Genetic testing for monogenic conditions provides a number of important benefits. Although therapies are unavailable for many rare genetic conditions, receiving a diagnosis can enable individuals to understand their condition and retain control of their lives. Predictive testing may also be useful if early diagnosis allows interventions or targeted care to reduce suffering or to aid future individual or clinical decision-making.

2.5 More recently, the sequencing of the human genome has generated large amounts of genetic data and research is now focused on developing a new generation of genetic tests for more common conditions, such as cancer and heart disease. However, progress in utilising this new knowledge in diagnostics has been much slower than expected. One reason for this is that common disorders are genetically complex and certain genes may also require interaction with particular environmental factors or with other genes in order to produce an effect. These problems with finding robust gene-disease associations raises serious questions about the extent to which it will be possible to develop new genetic tests for anything other than a few well characterised sub-sets of diseases, such as cancer.

2.6 Another form of molecular testing involves the use of biomarkers. These are normally proteins, but they can also be other molecules, such as fats or antibodies, and have the advantage of being able to report on conditions caused by a complex pattern of gene, environmental and behavioural interaction. As a consequence, protein biomarker

research has focused on more common conditions, such as neurodegenerative conditions, heart disease and cancer. However, at present relatively few tests are on the market (e.g. Alzheimer's disease, prostate cancer) and there are significant problems associated with the clinical utility of the information they generate.

2.7   With the possibility of future testing expanding beyond rare monogenic disorders there are various organisational issues that will need to be addressed. Routine predictive testing for common diseases would involve large patient numbers and place heavy demands on the existing health service infrastructure. In addition, sophisticated technologies and well-trained specialist staff will be needed to interpret test results. Finally, relatively little work has looked at the cost effectiveness of these molecular diagnostics and new methods of measuring their potential benefits need to be developed.

2.8   A number of important social, ethical, and legal issues are raised by the development of genetic testing and molecular biomarkers, including: informed consent and the consequences of testing for family members; privacy, confidentiality and the disclosure of test results; and the potential misuse of genetic information in insurance and employment. It is therefore important that these technologies are tightly regulated. However, no legislation governs the scientific validity and clinical utility of commercial genetic tests sold direct to the public in the UK.

2.9   As a consequence of the important barriers that face the development and adoption of genetic testing and molecular biomarkers the high hopes that followed the sequencing of the human genome have been replaced by a much more cautious view on the prospects for these technologies. It is now generally acknowledged that the development of valid, clinically useful tests for common conditions will take far longer than many people initially predicted. In the short term at least, it appears that genetic testing will provide benefits by allowing the characterisation of some diseases at the molecular level, predominantly aiding medical research rather than clinical diagnosis.

Chapter 3. The discovery and development of new small molecule drugs and the possibility of 'personalised' medicine

3.1 **The productivity crisis in the pharmaceutical industry.** Historically the process of pharmaceutical development has focused on producing drugs for large groups of patients. These drugs have generally been small organic chemicals ('small molecule' drugs) and are tolerably safe for the majority of users, although they often vary in effectiveness.

3.2 In recent years the industry has suffered from an ongoing crisis in both innovation and productivity in discovering and developing new drugs. A major reason for this is that in the last 20 years the financial cost of the drug discovery and development process has greatly increased and R&D spending by pharmaceutical companies has risen sharply. However, in the same period the time taken to bring a new drug to market has doubled, and now stands at 12-15 years. Furthermore, the number of new drugs reaching the worldwide market has been falling since the 1960s.

3.3 The process of drug innovation is extremely risky, with many compounds failing in development. Pharmaceutical companies have adopted a number of strategies to reduce the risk of failure and the associated financial losses. Much pharmaceutical research focuses on a limited group of drug targets, which have a tried and tested track record of clinical and commercial success (so called 'me-too' or follow-on products).

3.4 Since the 1980s pharmaceutical companies have grown increasingly reliant on a small number of 'blockbuster drugs' with sales over $1 billion a year. However, many blockbusters are follow-on products, usually aimed at common chronic diseases, which require the long-term treatment of patients. These markets are valuable, but are becoming increasingly crowded with competing products. Furthermore, patents on a significant number of blockbusters are close to expiry. This has prompted the search for new sources of innovative products and increasing investment in molecular biology, biotechnology and genomics.

3.5 The first successes of biotech were biopharmaceuticals in the 1980s. However, only following the advent of the Human Genome Project (HGP) and the coming of genomics in the mid-1990s did new technologies based on biology start to have a significant impact on the process of creating new medicines within the mainstream pharmaceutical industry. The main attraction of genomics has been the promise of discovering thousands of new and potentially novel targets for the development of small molecule drugs. This prospect has stimulated billions of dollars of pharmaceutical industry investment in genomics.

3.6 This strategy was based on the assumption that new drugs based on novel genomic targets would be better candidates for entering clinical trials. However, this has proved more difficult than first expected and validating the exact role these genes play in disease and developing new drugs based on this knowledge has been difficult and will take a great deal of time and effort.

3.7 **Pharmacogenomics and pharmacogenetics.** In the last five years the focus of post-genomics research has been on the function and expression of genes, and on studying the variations within and between different human populations. This has sparked

growing interest in the two closely related areas of pharmacogenomics and pharmacogenetics.

3.8   Pharmacogenomics is concerned with providing a comprehensive, genome wide assessment of the effects of pharmacological agents on gene expression patterns. In particular, it has been helping understand the precise molecular mechanisms involved in causing particular diseases. This information has been successfully used to develop a new group of targeted (or so called 'designer') cancer therapies.

3.9   Pharmacogenetics is the study of the genetic basis of drug response. One of the potential advantages of pharmacogenetics lies in matching the natural variation in a person's genetic make-up (their genotype) to their response to specific pharmaceutical products. This might enable the prescription of medication to be tailored to an individual's genotype, allowing the development of so-called personalised medicine. The introduction of pharmacogenetics rests on two key ideas: 1) The stratification of patient populations according to their response to a particular medication. 2) The stratification of diseases into specific subtypes that are categorised according to genomic criteria. This has started to occur in relation to a number of common diseases, such as certain cancers, and can result in improved diagnosis.

3.10   A key factor in the potential development of pharmacogenetics is that disease and patient stratification would also involve the segmentation of drug markets. This fundamentally threatens the cornerstone of pharmaceutical industry profits - the blockbuster drugs. Fresh knowledge about human genetics has been heralded as being able to greatly reduce the costs of drug development and supply thousands of new drug targets. To gain these benefits, however, pharmaceutical companies may have to drastically restructure operations to account for genetic variability.

3.11   A series of discrete options for the clinical and commercial application of pharmacogenetics can be identified, including improving drug discovery; improving the safety and efficacy of drug in development; and improving the prescription of licensed drugs.

3.12   A small number of pharmacogenetics products are already on the market, the most common of which are tests to detect variants in drug metabolising enzymes for use in pre-prescription genotyping to prevent adverse drug reactions (ADRs). One of the best-known examples of genes that affect the rate of drug metabolism is the Cytochrome P450 (CYP) gene family, variants of which are involved in metabolising 25% of all currently prescribed medicines. Knowledge of a patient's CYP status can be a useful prescribing aid. Other current tests are attached to a particular marketed product. These tests are used to stratify patients to identify particular response groups and aim to focus treatment where it is most effective. This helps avoid unnecessary drug use.

3.13   A range of pharmacogenetic tests are in development and are aimed at either improving the use of existing, approved drugs such as statins, chemotherapy drugs and treatments for rheumatoid arthritis or are intended to be developed in concert with new drug products.

3.14   Pharmacogenetics is inextricably linked to the process of genetic testing. To be of clinical utility, tests must be accurate in predicting a patient's status, should not

produce an unacceptable level of false positive or false negative results, and can be applied within and across different populations. Ultimately, successful tests should be easy to perform, reliable, relatively inexpensive and easily interpretable, if they are to be incorporated into clinical practice.

3.15 The application of the technology will also need to be cost-effective. For drug companies, pharmacogenetic testing offers the possibility of targeting new drug development at specific genetic populations where they will be most efficacious. This may help get more drugs approved and possibly allow smaller clinical trials. Healthcare organisations could also potentially make cost effective use of pharmacogenetic testing through reducing the use of ineffective therapies, but this must be set against the cost of genotyping, as well as counselling, additional clinical visits and appropriate post-test follow up.

3.16 Pharmacogenetics shares many of the same ethical considerations, such as privacy, informed consent and confidentiality, as other forms of genetic testing. In addition, there are some ethical concerns unique to the technology, including a) the creation of new therapeutic 'orphan populations' who have no access to new and more effective therapy; b) greater risks from 'off label' prescribing; c) inequity, stigmatisation and discrimination arising from patient and disease stratification; d) the blurring of the boundary between pharmacogenetics and disease susceptibility testing; and e) a link to racial profiling for prescribing which may reinforce discredited biological notions of race.

3.17 Within the pharmaceutical industry there are major concerns that pharmacogenetics will undermine the blockbuster model and replacing it with more specific drugs aimed at patient sub-populations. There is also anxiety that new regulatory requirements may increase the regulatory hurdle, restrict product labels and make genetic testing mandatory for a much larger number of therapies. Similarly pharmaceutical companies are unlikely to be motivated to invest in genetic tests for successful drugs already on the market, as this is likely to reduce the market for their products. A number of smaller diagnostic firms are looking to develop pharmacogenetic tests for a number of important and well-established drugs. These could offer real public health benefits. However, there is a real danger of 'market failure', with many of these potentially valuable tests never being introduced into clinical practice due to lack of resources.

Chapter 4.   New biological therapies

4.1   Biological drugs and therapies are derived from the molecular and cellular materials of the human body and differ in important ways from other pharmaceutical products. In particular, many biologicals are not orally administered and this significantly limits their clinical use.

4.2   The discovery of recombinant DNA in the 1970s ushered in the era of biotechnology. This allowed the production of proteins on an industrial scale and the resulting therapeutic proteins formed the first wave of new biological therapies. The impact of the Human Genome Project (HGP) has been the discovery of a large number of human genes, but understanding their function is occurring at a slower pace than first hoped for. In the long term this new knowledge provides the opportunity for a greater range of biological therapies. However, some biological technologies raise important ethical, legal and social concerns and the successful implementation of these novel therapies in clinical practice may demand the creation of new infrastructures and wider access to specialist skills and facilities.

4.3   **Therapeutic proteins.**   Proteins can act as therapeutic agents because they have evolved naturally to provide a specific biological function. A number of early therapeutic proteins failed clinical trials because they were altered during manufacturing, resulting in their rejection by the immune system. These problems have been largely overcome by the development of mammalian cell culture techniques.

4.4   As proteins are naturally occurring their use might be expected to avoid many of the side effects of synthetic small molecule drugs. They also perform specific biological functions and are ready-made therapies for deficiency disorders, such as diabetes. However, it has proved much harder than expected to develop new products, with many proteins failing to demonstrate sufficient efficacy in clinical trials.

4.5   There are currently over 50 different recombinant protein therapeutics available on the European and US markets. The majority of these are prescription drugs for natural protein replacement therapy. The global market for protein therapeutics in 2005 was in excess of $37 billion, represented some 8% of all medicines sold and has an annual growth rate of ~15%. The majority of the most widely used therapeutic proteins are for chronic conditions poorly served by conventional therapy, including cancer, arthritis and a number of rare genetic disorders.

4.6   A range of new therapeutic proteins are currently in late stage development. These include treatments for cancer neurological disorders, cardiovascular diseases, autoimmune disorders and skin conditions. Despite this, only a small number of new and genuinely novel therapeutic proteins reach the market each year. In the last 20 years only 12 therapeutic proteins have been launched which had sales of over $500m a year in 2004, and only five of these were launched in the last decade. There are few signs that this rate of innovation is increasing.

4.7   Therapeutic proteins are already well established in the clinic and are often the best or only course of treatment in the chronic care of patients with life-long protein deficiency conditions. Most do not require any specialist training or expertise and this means that patients do not require frequent contact with physicians. Many protein

drugs have a relatively short half-life in the body and have to be given at least once a week. This results in significant side effects, problems with patient concordance and has stimulated the development of longer-lasting products and formulations. Furthermore, many therapeutic proteins are also very expensive.

4.8   The main focus of the future development of therapeutic proteins is the creation of so called 'next generation' products based on protein engineering. This will allow specific changes to alter its characteristics in a beneficial way (last longer, have fewer side effects and can be given less frequently). A number of genetically altered products are already on the market and more are in late stage development. Other innovations include attempts to deliver protein drugs orally or in an aerosol in order to avoid injection. Furthermore, several of the most important protein therapies are shortly about to come off patent, thus opening up the possibility of cheaper 'biogenerics'. However, regulatory agencies in Europe and the US have yet to establish the marketing approval framework for the development of these products.

4.9   **Monoclonal antibodies.** Antibodies are proteins produced by cells of the immune system. Their function is to recognise foreign or toxic material, marking it for elimination from the body. Monoclonal antibodies (MAbs) are antibodies that are structurally identical to each other, are highly specific and can accurately bind to particular targets involved in causing disease. When MAbs were first isolated in 1975 they were heralded as a potential 'magic bullet' for treating disease. However, harnessing the abilities of monoclonal antibodies was not as easy as had been initially thought and many early products failed during clinical testing. It is only recently, with the development of fully humanised MAbs that the initial promise of the technology has started to be realised.

4.10   There are currently nearly 20 monoclonal antibodies produced by recombinant DNA technology (chimeric, humanised and fully human) and a further ten monoclonals of murine origin on the market in the US and Europe. The biggest sellers, such as Remicade and Rituxan, have annual global sales of over one billion US dollars. In terms of diseases, most target chronic conditions, including different forms of cancer, rheumatoid arthritis, asthma and suppressing graft rejection after transplantation. Monoclonal antibodies are mainly administered in secondary care to treat patients with long term or ongoing conditions. They are given in the context of specialist services, but do not require a great deal of extra knowledge or infrastructure. However, they are expensive.

4.11   The future of monoclonal antibody technology looks promising, as there are a significant number of MAbs in late stage clinical development. Many monoclonal antibodies receive FDA fast-track status for US approval and generally gain rapid regulatory approval. The range of applications for monoclonal antibodies also continues to expand.

4.12   The global market for monoclonal antibodies was estimated to be $11.2 billion in 2004 and had an annual growth rate of over 40% between 1999-2004. A steady stream of new products are anticipated to receive marketing approval in the next few years and the introduction of fully humanised MAbs should significantly help the development of future products. In addition, new technologies and antibody engineering promise to create even greater antibody diversity and higher therapeutic specificity. Despite the renewed clinical and commercial optimism surrounding

MAbs, it should not be forgotten that it took over 25 years from the discovery of monoclonals for them to start to realise their full potential.

4.13 **Cancer vaccines.** All vaccines are based on the idea of stimulating the immune system to fight off disease. Therapeutic vaccines are intended to work in the same way to target established chronic non-infectious conditions, such as cancer. Existing therapies for treating cancer often cause considerable damage to healthy tissues and can cause significant, harmful and unpleasant side effects. Furthermore, surgery to remove a tumour is not always successful, as the cancer may have spread to other parts of the body. Cancer vaccines could utilise the specificity of antibodies to attack tumour cells in different sites, thus avoiding many side effects and complications.

4.14 There are currently no approved cancer vaccines in the UK or US, although one product is licensed in Canada. There are a variety of strategies for producing and delivering cancer vaccines. Most therapies target a specific type of cancer, such as prostate or breast cancer. Vaccine developers are split between those producing 'universal' therapies, which could be applied 'off-the–shelf' to all patients suffering from a particular cancer, and 'personalised' treatments that are tailored to an individual's tumour cells. In 2004 there were 24 Phase II clinical trials and ten Phase III trials of cancer vaccines ongoing in the US and many more in early investigative phases.

4.15 A variety of these cancer vaccine strategies raise important safety and implementation issues. In addition, a significant barrier is the difficulty in developing a personalised vaccine, which would require specialist facilities, highly trained staff and elaborate quality assurance systems to produce treatments on an individual basis. There is regulatory uncertainty surrounding this type of product and it is not clear that bespoke production would be economically viable or commercially attractive. As a consequence of these uncertainties and a long history of failed clinical trials it seems unlikely that many cancer vaccines will enter routine clinical practice in the short to medium term.

4.16 **Stem cell therapy.** A very small sub-set of the adult cells in many tissues retain the ability to divide indefinitely; these are known as stem cells (SCs). The idea of cell therapy is to use these immortal stem cells to replace damaged or diseased tissues. Embryonic stem cells (ES cells) are a unique form of stem cells found in the early embryo that can give rise to almost all the cell types in the body. These can be derived from a number of sources, including so called 'spare embryos' created during IVF procedures and embryos specifically created for research purposes. ES cells can also be created by 'therapeutic cloning', which involves fusing an adult cell with an altered egg cell to create an artificial embryo. In contrast, adult stem cells can only normally differentiate into a limited number of cell types.

4.17 Stem cell therapy has been heralded as a way to treat degenerative diseases, caused by progressive cell death or damage, such as Alzheimer's and Parkinson's disease, MS and heart disease. At present there is no cure for these conditions and patients can only look to treatments that will alleviate symptoms, but stem cells could offer the real prospect of a cure. Adult stem cells and those produced by therapeutic cloning hold the additional benefit of avoiding rejection by the immune system.

4.18   The only stem cell therapy procedure currently in routine use is the isolation and transplantation of haematopoietic stem cells following chemotherapy for the treatment of leukaemia and other cancers. Very few other potential therapies are close to introduction into the clinic as none are in phase III trials, however, a wide range are in early development including treatments for cardiovascular disease, neurodegenerative conditions, diabetes, arthritis and a range of cancers.

4.19   One of the major technical problems facing the field is that simply applying stem cells to the target tissue in the hope of spontaneous regeneration is not a guarantee of therapeutic efficacy. As a consequence, much current effort is focused on controlling the differentiation of stem cells into specific adult cell types. One of the major advantages of embryonic stem cells is that they are easier to grow and appear to have more potential for forming different cell types. However, due to the major ethical issues that surround their use, there is considerable interest in developing adult stem cells as therapies. A third type of stem cell can be harvested from the blood taken from the umbilical cord when a baby is born. These now are used as an alternative to haematopoietic stem cells derived from bone marrow. Researchers are also hoping to find the growth factors that control the mobilisation, division and differentiation of stem cells into various tissue types. This might lead to the creation of drugs that would activate stem cells without having to remove them from the body.

4.20   Stem cells therapies may involve highly specialist staff and equipment, are likely to be restricted to tertiary care and are expensive. However, unlike the use of therapeutic proteins and monoclonal antibodies, stem cell therapy may only need to be applied on a limited number of occasions. In the longer term, researchers and companies are looking to develop alternative strategies. These include the creation of 'universal' cell lines, which could be transplanted into a wide range of patients and would avoid the need for local cell processing. However, the regulatory framework governing the manufacture and use of all types of stem cell products is still emerging.

4.21   Stem cell research has been surrounded by controversy, mainly because of the use of embryonic stem (ES) cells. In particular, there continues to be a major social and ethical debate about the morality of using embryos in scientific research. Opponents of the use of embryonic stem cells cite the existence of adult stem cells as a less controversial alternative, but it remains to be seen whether adult SC's retain sufficient developmental potential to generate effective therapies.

4.22   Cell therapy remains a promising long-term prospect for medical treatment of currently incurable conditions, but there are significant technical and ethical problems to be overcome before this can occur. It is therefore unlikely to be a clinical option beyond its established use in cancer treatment in the near future.

4.23   **Gene Therapy.** There are two types of gene therapy. Somatic gene therapy is the delivery of functional genes to somatic tissue (i.e. not the sperm and eggs) for the treatment of disease. The therapy therefore only affects the person to whom it is given. In contrast germ line gene therapy is aimed at genetically altering germ cells for the treatment of diseases in future generations. For both ethical and safety reasons, germ line therapy is not being developed in humans at present.

4.24   Gene therapy has been heralded as having the potential to be one of the most important developments in medicine in the next century. In principle, gene therapies

could be highly targeted, have fewer side effects and be applied to a number of important chronic diseases that are poorly served at present. More importantly, in the long-term, gene therapy holds out the promise of a permanent cure for a number of genetic diseases. However, in the short-term at least, it is likely to be limited to the treatment of a relatively small number of rare inherited conditions, HIV infection and different forms of cancer.

4.25   All gene therapies involve the use of a delivery system (or vector) to transfer the therapeutic gene. These can be either viral or non-viral (e.g. a fat molecule) in origin. In the 1,000+ clinical trials conducted by the start of 2006 viral vectors have been used in over 60% of all clinical studies. Furthermore, there are two distinct ways in which these gene transfer methods can be applied. *Ex vivo* gene therapy is where the modification of the patient's cells occurs outside the body. *In vivo* gene therapy is where the genetic alteration of the cells occurs by direct administration of the therapy to the patient, mainly by injection. *Ex vivo* therapy requires more intensive laboratory and cell processing procedures, but is a generally easier means of undertaking efficient gene transfer. In contrast, *in vivo* therapies are more technically demanding but are more clinically and commercially attractive, as they are easier to manufacture and use in practice.

4.26   The first officially sanctioned clinical trial of gene therapy was carried out in the US in 1990 for the treatment of a rare genetic disease. By 2006 1,145 gene therapy trials had been organised internationally, with two-thirds of these being for cancer. The first successful cure was announced in 2000 following *ex vivo* therapy in a small number of children suffering from a very rare genetic disorder. Despite this, there are no approved products in either the US or Europe, and only one gene therapy product has been successfully brought to market anywhere in the world, for treatment for head and neck cancer in China.

4.27   Gene therapy is a form of human genetic engineering and often involves testing highly experimental treatments and novel practices in human subjects. The prospect of developing a successful gene therapy has held great allure for pioneering researchers. However, the race to be the first person to make it work, as well as the very significant financial interests involved, has led to a series of scandals. As a consequence it has become one of the most controversial areas of modern medicine, has been the subject of much ethical debate and is tightly regulated. Furthermore, there are major safety problems associated with a number of the main viral vector systems. These have led to death or serious illness in a small number of patients involved in testing therapies, and have been a major setback for the field.

4.28   Gene therapy still remains at an early stage of development, despite a great deal of investment and clinical research. Some notable successes have been achieved, but the very serious safety problems that have arisen in recent years cast a long shadow over the future of the field. It therefore appears that despite its long term potential, only a few products are likely to enter routine clinical use in the medium term.

Chapter 5. The changing context of medicines development and use

5.1.   A number of major changes are occurring in the broad environment surrounding the development and use of new drugs and diagnostics. The main changes and new policy initiatives likely to affect the development, licensing, marketing, distribution, and use of new medical technologies are summarised below.

5.2   **The changing pharmaceutical industry.** Over the last two decades the industry has faced a number of important challenges, including: globalisation and international harmonisation; healthcare cost containment; an ageing population; patent expiries and the growth of generics; decreasing R&D productivity; and the rise of biotechnology. In response to these challenges a number of important changes have occurred, including:

- Industry consolidation
- Greater product focus on the management of chronic diseases
- Increasing R&D expenditure
- Major investment in biology and biotechnology
- R&D outsourcing and the growth of the biotechnology industry

5.3   **The changing pharmaceutical market place.** Alongside changes in the structure of the pharmaceutical sector there have been significant shifts in the pricing, distribution and marketing of prescription medicines. These have resulted in the creation of both new markets and new forms of demand and include:

- Attempts to reduce the cost of medicines in the UK through changes to the Pharmaceutical Price Regulation Scheme
- New regulations controlling the price of generic medicines sold to the NHS
- Changes to the organisation of community pharmacy and the development of e-pharmacy
- Greater emphasis on over-the-counter medicines
- Increasing direct to consumer advertising

5.4   **The changing NHS.** There has been a process of near constant change to the structure and organisation of the NHS over the last 20 years. Despite this, relatively few policies have had a major impact on the development and overall consumption of medicines in the UK. However, specific initiatives are impacting on the use of particular drugs and diagnostics, and include:

- The implementation of national service framework guidelines
- The increasing use of health technology assessment
- The development and implementation of National Institute for Health and Clinical Excellence (NICE) guidelines
- Greater investment in the development of genetic services

5.5   **Changing professional practice.** Recent policy changes have had a considerable impact on the mode and nature of professional practice within the health service. The NHS Modernisation Agency is driving through a programme of reform based on a national set of protocols for dealing with common conditions and determining which

staff are best equipped to deal with them. Initiatives aimed at changing professional practice include:

- New training and career development pathways to enable appropriately qualified staff to expand their roles
- Primary care centres where general practitioners, opticians, dentists, pharmacists and social care workers are grouped together under one roof
- A new role for pharmacists, with a focus on the greater utilisation of their skills and a move from dispensing medicines towards providing an extended range of services

5.6 **Changes to the regulation of new medical technologies.** The way in which genetic research and the development of healthcare products is regulated can have a major impact on the process of medical innovation. A number of important changes have occurred in recent years to both the governance of research and the regulation of new medicinal products. These include:

- Reform of the oversight of human genetics research in the UK through a strengthening of the non-statutory advisory system
- Greater European regulation of medicines through the work of the European Medicines Evaluation Agency (EMEA)
- New medical devices regulations

5.7 **The development of policies to support the development of innovative health technologies.** The promotion of science, technology and innovation has become a major priority for government in recent years, especially in the field of biomedicine and biotechnology. These have included measures to:

- Strengthen research and development
- Improve the competitiveness of the pharmaceutical and other healthcare industries
- Foster innovation and stimulate technology development and transfer
- Strengthen partnerships between the NHS, industry, the universities, Research Councils and other funders to promote synergy in the science base
- Improve the research infrastructure in the NHS
- Introduce new arrangements to support science and clinical research in the NHS

Chapter 6. Summary and conclusions

6.1   Trying to assess the future development of new technologies is a demanding and problematic endeavour. This is due to the wide range of factors that determine success and the high levels of technical, commercial, clinical and regulatory uncertainty that often mark early medical innovation. Because of this, previous work on technological forecasting has established that it is very difficult to assess accurately the prospects for an emerging technology much more than three years into the future.

6.2   **Criteria for successfully developing new medical technology.** To help guide the analysis of early innovation, a conceptual framework derived from work in the sociology of technology has been used. In particular this draws on the idea that in order to be successful, emerging technologies must meet a series of important criteria:

- Scientific proof of principle
- Demonstration of safety and therapeutic efficacy
- Successful adoption (integration into clinical practice)
- Establishment of a viable business model for their commercial exploitation
- Resolution of any important social and ethical issues
- Creation of a stable regulatory framework
- Enrolment of public support and legitimation

6.3   The idea that early biomedical innovation involves a complex series of steps is captured in the idea of 'entrenchment'. To become entrenched into routine healthcare a new medical technology must be safe and effective, but must also be available as a commercial product, fit into established working practices, command the confidence of patients and be regulated in an enabling manner. Using this framework it is possible to analyse the extent to which the technologies described in this report have become, or are in the process of becoming entrenched. They can be divided into three broad groups:

a.   Technologies that are well entrenched in the clinic

- Genetic testing for monogenic disorders
- Therapeutic proteins
- Monoclonal antibodies.

The medium term prospect for an expansion of these technologies is very promising and they raise few new social, ethical or practice issues.

b.   Technologies that are starting to become entrenched in the clinic

- Pharmacogenomic drugs
- Pharmacogenetic drugs/tests
- Genetic tests for common conditions
- Adult stem cell therapies.

An expansion of these technologies in the medium term is therefore likely. However, each of them has yet to be fully entrenched in a mature market or established set of clinical practices. They still face significant technical difficulties

and, with the exception of pharmacogenomic drugs, they will also have to overcome a number of commercial, clinical, ethical and regulatory difficulties.

c. Technologies that have yet to successfully enter the clinic

- Gene therapy
- Cancer vaccines
- Embryonic stem cell therapies.

Each of these technologies face very significant problems at present and are unlikely to enter the market in anything other than first proof of principle products in the near future.

6.4 **Factors shaping the adoption of genomic medicine in the UK.** A number of changes in the broader environment in the UK are shaping the development, diffusion and use of emerging medical technologies.

a. *The changing pharmaceutical industry*: Current trends are likely to lead to continuing emphasis on blockbuster drugs, a greater focus on chronic diseases management, and further investment in biotechnologies. Taken together this suggests that the pharmaceutical industry will continue to invest heavily in genetic and biological technologies, especially those that are close to its established product focus. However, significant commercial uncertainty surrounds the development of drugs and diagnostics for segmented drug markets.

b. *The changing pharmaceutical market place*: It seems unlikely that changes in the regulation of the price of prescription drugs, the reform of community pharmacy or the shift to OTC medicines will have any significant impact on the development and diffusion of new genomic medicines. Furthermore, very few of these technologies will be available in primary care settings and none are likely to be offered as OTC products in the near future. The increasing emphasis on direct to consumer marketing is unlikely to have an impact on the demand for new genome-based drugs in the UK.

c. *The changing NHS*: The introduction of National Service Frameworks and NICE appraisals and guidelines are proving to be an effective mechanism for the diffusion of best practice. This is likely to significantly increase demand for specialist therapies if they can be shown to add value and be cost-effective. The development of genetic services should help the adoption of several genetic and biological technologies. In particular, the reform of NHS genetic laboratory services is likely to have a significant impact on the future growth of pharmacogenetics and genetic testing for both monogenic and common conditions.

d. *Changing professional practice*: Whilst the changing role of community pharmacy is likely to provide greater patient access to many established medicines, it is unlikely to have a significant impact on the use of new genetic and biological technologies as these are mainly used in secondary and tertiary care. Hospital pharmacists may play a greater role in the application of some of these emerging therapies, but this is unlikely to have a major impact on demand.

e. *Changes to the regulation of new medicines*: A number of the technologies described in this report are surrounded by important ethical debates. Recent moves to

strengthen the formal oversight of human genetics research in the UK may play an important role in resolving outstanding ethical debates and ensuring public confidence. There is little evidence to suggest that the EU centralised approval process for biotechnology products are a significantly barrier to innovation, but there still remains regulatory uncertainty about the introduction of pharmacogenetics and the introduction of products based on cell processing. However, regulators are already playing a key role in promoting the adoption of pharmacogenetics.

f. *Government support for the development of innovative health technologies*: A clear commitment has been given to promote the further development of innovation in the NHS and the growth of the UK biotechnology industry. This has been articulated in a coherent series of policy measures that seek to increase funding and strengthen both the science base and the infrastructure for undertaking clinical research. This should help facilitate the process of translating basic research into viable new technologies and the creation of a clinical evidence base.

6.5   Most of the forces listed above are operating to promote innovation in this area. The only one that has been seen to inhibit the diffusion of innovative 'high tech' medicines is the working of NICE, but even here initial guidance restricting the use of several new products was overturned and a number of measures have promoted the diffusion of new technologies for specific applications. It therefore appears that the overall environment in the UK is very favourable for the discovery and development of new genetic and biology-based therapies and diagnostics.

6.6   **Expectations and innovation in genomic medicine.** The field of genomic medicine is marked by high hopes for its future. This report has attempted to present a detailed analysis of the current state of development of these key emerging technologies and assess their prospects for further growth in the medium term. Significantly, it appears that there will be a continuing, but modest, stream of new medicines and diagnostics reaching the market. It is clear that this level of progress falls a long way short of the high expectations that surround this area. However, high expectations are integral to the process of developing new genetic technologies, but they can cause major problems if they are very unrealistic, as false hopes may distort funding and research priorities and ultimately lead to professional disappointment and public disillusionment. It is therefore important to ensure that there is some linkage between public expectations and progress in the laboratory and clinic.

6.7   In order for effective public policy to be developed in the field of genomic medicine, two things need to change; firstly, a more realistic set of expectations about the speed and scale of innovation needs to be adopted by all stakeholder groups; and secondly, a different model, which views biomedical innovation as a slow and incremental process, should be used to inform public discussion and policymaking. In general, it is not the lack of public support, adverse media reports or excessive regulation that holds back the development of new medicines, but the very significant scientific and technical problems involved.

6.8   **Implications for pharmacy.** If this model of technical change is adopted then the emphasis of policy is not simply on anticipating the impact of new genetic technologies, but on helping them come into being. The main genetic technologies likely to affect community pharmacy in the medium term are therapeutic proteins, pharmacogenetic drugs and tests, and new molecular biomarkers. Of these,

pharmacogenetic tests are likely to have the most significant implications and the profession's response to the challenges surrounding the introduction of this technology could form a model for how it might engage with these innovations more generally. Taking this as a case study, the following policies might be adopted relating to pharmacy:

- Translating scientific research findings on pharmacogenetics into working technologies and new clinical practices
- Building NHS capacity and developing new services in pharmacogenetics
- Creating new technical and organisational infrastructures to support pharmacogenetic testing
- Increasing professional knowledge and training in pharmacogenetics
- Establishing new governance regimes to control the use of pharmacogenetic testing

Chapter 1. Introduction: the promise of genetics, genomics and molecular medicine

The sequencing of the human genome has sparked great interest in what many have called 'genomic medicine'. Advocates claim that knowledge of the genome will usher in a new era in medicine, which will focus on prevention rather than cure and personalised treatment based on new and more powerful therapies. These expectations are articulated in many places including newspaper articles, TV programmes, industry conferences and government policy documents. For example, the recent UK Genetics White Paper claimed that:

> *"Our genes play a fundamental role in determining our health and our response to healthcare. Six out of ten people are likely to develop a disease that is at least partially genetically determined by the age of 60. Greater knowledge of genetics will have a major impact on our understanding of human illnesses and herald a step change in disease prevention, diagnosis and treatment. Although there are difficult moral issues raised by genetic advances we see enormous overall potential benefits for patients."* (Department of Health, 2003a, p11)

This prospect is often couched in terms of a 'revolutionary' change, underscoring the idea that the genomic era will bring about a different sort of medicine. Specifically, these hopes are attached to a series of new technologies and clinical practices:

> *"Genetics offers enormous potential to improve our health and healthcare - more personalised prediction of risk, more precise diagnosis, more targeted and effective use of existing drugs, new gene-based drugs and therapies, and prevention and treatment regimes tailored according to a person's individual genetic profile."* (Department of Health, 2005)

These statements embody a number of important assumptions about the future of medicine. These are that genetic changes (mutations and polymorphisms) play a central role in causing many common diseases and determining the risk of getting these conditions, that genetic knowledge will form the basis for a range of diagnostic and therapeutic technologies, and that these advances raise important social and ethical issues. These underpinning beliefs have now become a taken-for-granted part of much policy and ethical debate, and are often uncritically accepted.

In terms of specific technologies, genomic medicine falls under three broad headings:

a. The development of new gene-based diagnostics for common conditions: Genetic studies allow researchers to dissect many common diseases in order to identify any underlying genetic component. Already a large number of population based association studies are underway to identify susceptibility genes and genetic risk factors in a number of common disorders, such as, cancer, heart disease, arthritis and depression. The identification of genetic risk factors in common diseases opens up the possibility of more accurate diagnosis using new DNA based tests. In particular, it is hoped that the accurate sub-classification of common disorders (so called 'disease stratification') will enable more targeted and effective therapy.

b. The introduction of pharmacogenetics or so called 'personalised medicine': A compelling hope for genomic medicine is the possibility of designing treatments for

individual patients, rather than depending on the current 'one size fits all' model of therapy. In particular, this builds on the idea that people respond differently to medicines according to their genetic make-up (genotype), so that in the future treatment will be guided by individual genetic profiles based on pharmacogenetic DNA testing. Allan Roses, a senior executive at GlaxoSmithKline, admitted in December 2003 that most drugs currently on the market only work in 30-50% of the population (Conner, 2003). Furthermore, it is widely recognised that as many as another 30% of patients given certain common medicines may suffer some form of side effect. Pharmacogenetics therefore holds the possibility of improving both patient safety and the efficacy of treatment by ensuring that drugs are only given to those patients who will respond well to therapy and who will not suffer an adverse drug reaction (ADR).

c. The creation of novel therapies: A number of gene and cell based therapies are currently under development, including gene therapy and the use of adult/embryonic stem cells, for the treatment of a wide range of diseases. These build on the established tradition of biological drugs, which include protein therapeutics (e.g. insulin) and monoclonal antibodies. Novel small molecule 'pharmacogenomic' drugs, such as Glivec, which target a particular genetic sequence, are also being developed. It is hoped that these new therapeutic modalities will address many clinical needs that are currently unmet, most notably in chronic degenerative conditions.

The broad prospect of genomic medicine has been backed by massive public and private investment in the last fifteen years. It has, in large part, inspired the creation of several thousand small biotechnology firms internationally since the early 1990s and stimulated the pharmaceutical industry to invest billions of dollars in genomics related technology over the same period. In addition, government and charitable funding agencies have spent billions of dollars on genomics related research in both Europe and North America, for example, it is estimated that over $3 billion has been invested in gene therapy R&D alone since 1990 (World Economic Forum, 2001). As well as the anticipated health benefits, genomics is also being increasingly seen as a key element of the new knowledge based economy, with analysts predicting the creation of thousands of new jobs in the biotechnology sector across Europe. This combination of expectations is neatly summed up by the sub-title of the UK Biotechnology, Innovation and Growth Team's (BIGT) report *Bioscience 2015* which claims that these advances will be *"Improving National Health, Increasing National Wealth"* (BIGT, 2003).

Assessing the implications for the future development of healthcare, the use of medicines and pharmacy practice

If these hopes are realised, the rise of genomic medicine is likely to have major implications for the future development of healthcare and the work of all professional groups in the health service. It is therefore important that a careful assessment is made of the current development and medium term prospects for this group of technologies in order to help guide policy and inform the work of professional bodies such as the Royal Pharmaceutical Society.

Specifically, this report has been commissioned to inform the development of the next phase of the Pharmacy Practice Research Trust's *Medicines and People* programme, which is designed to deliver the knowledge needed to understand and develop polices relating to the complex process of: *Getting the right medicine to the right person at the right time in a manner that meets the needs and expectations of the individual who will take it.*

This report aims to:

1. Briefly describe the main scientific and technical advances in the area of genomic medicine;
2. Assess the prospects for the short and medium term development of these technologies, their potential benefits and possible social and ethical implications;
3. Identify the main changes in policy, practice and the organisation of healthcare that might be needed to accompany their introduction;
4. Identify key areas of research that would inform the development of policy relating to the implementation and uptake of the scientific and technical advances in genomic medicine, focusing on the main themes in the Medicines and People programme.

To achieve this the report will draw on evidence from scientific, technical and commercial literature, as well as a number of recently completed and ongoing research studies conducted at the Institute for the Study of Genetics, Biorisks and Society (IGBiS), University of Nottingham (see www.nottingham.ac.uk/igbis). Each of the next three chapters will describe the main groups of technologies outlined above, which fall under the broad heading of genomic medicine. A short technical description will be given of the therapies and diagnostics in each group, and the specific types of products in use or in development, paying particular attention to those being commercialised by the biotechnology and pharmaceutical industries. This will be followed by a consideration of the implications of these technologies for clinical practice, as well as the main social, ethical and regulatory issues raised in each case. Finally, some conclusions will be drawn about how the potential of each group of technologies might best be realised. Chapter 5 will then examine the changing context of the development, marketing and use of new drugs and devices and will identify some of the main factors shaping innovation in this field. Finally, Chapter 6 will summarise the results of the four empirical chapters and draw out the main conclusions for policy and practice.

Chapter 2.   New molecular diagnostics: genetic tests and protein biomarkers

2.1   What are genetic tests?

Genetic testing generally refers to the direct testing of an individual's DNA, normally where there is some evidence of disease. This is distinct from genetic screening, which involves testing families or populations where there is no prior evidence of disease. Testing can involve looking for changes in chromosome numbers or structure (cytogenetic testing) or analysing changes (mutations or polymorphisms) in the molecular sequence of the DNA itself (molecular testing). Different types of analysis are used for the diagnosis of particular conditions. For example, karyotyping, which analyses the microscopic structure of chromosomes for large-scale rearrangements or deletions is used when testing for Down's Syndrome, which is caused by an extra copy of chromosome 21. In contrast, genomic or gene-based tests (molecular testing) use blood or other tissue samples to look for DNA changes within the sequence of specific genes. Current uses of genetic tests include:

Confirmatory diagnosis
A large number of rare diseases are caused by a single 'faulty' gene. These are known as monogenic conditions and the NHS currently offers around 300 molecular tests for rare inherited disorders, such as cystic fibrosis. These tests are responsible for the vast majority of genetic testing services currently available. Although the results of such diagnostic tests have implications for long-term prognosis, their main purposes are to provide information about a patient's current state and in some cases to support the reproductive choices of couples at risk. Individuals inheriting a specific genetic change associated with many monogenic disorders will often develop the associated condition, although this may vary depending on the 'penetrance' of the disorder.

For example, the detection of the mutant FMR1 gene is the definitive diagnosis of Fragile X syndrome. In this condition the deficiency of a gene located on the X-chromosome (of which males have one copy and females two) leads to mental impairment and hyperactivity in affected children. It is estimated to affect one in every 2,000 boys, making it one of the most common causes of mental impairment. Without genetic testing early diagnosis is difficult because it relies on interpreting subtle physical signs, such as a typically elongated face and large ears, and can be hard to distinguish from other causes of mental impairment. Early intervention and special education programmes, including speech and physical therapy are often beneficial (www.yourgenesyourhealth.org, 2004) and provide a strong rationale for early genetic testing in children who may have Fragile X.

In addition to confirming the diagnosis of rare inherited disorders, genetic tests are now also used to characterise leukaemias and some solid tumours. This is done by analysing acquired genetic changes (somatic mutations) that have occurred as the cancer has progressed, and can help characterise the type, stage, and origins of the disease. This information is useful in the management of therapy.

Carrier testing
Carrier testing is used to identify the presence of a genetic change in healthy individuals that may have implications for children or other relatives. In the case of inherited disorders, the deleterious gene may be recessive i.e. it may only have an effect if an individual has two copies, one inherited from each parent. Individuals carrying one copy of the faulty gene will

have no symptoms themselves, but could pass the condition on to their children if their partner is a carrier as well. Certain ethnic groups, such as Ashkenazi Jews, carry a higher incidence of certain rare inherited monogenic disorders (e.g. Tay Sachs) and community-based carrier screening programmes have been established to reduce the incidence of affected children.

Prenatal/Neonatal Screening

Prenatal testing is performed during pregnancy to assess the health status of a foetus. Individuals with a family or medical history indicating they may be at increased risk of having a child with an inherited genetic condition can be screened for the presence of genes that may cause or influence the condition. If a serious condition is identified, the woman can be given genetic counselling and offered the possibility of a termination. Neonatal screening is used to identify babies who have an increased chance of developing a specific genetic disorder so that treatment can be started as soon as possible. For example, newborn infants who have been identified as having the genetic condition phenylketonuria (PKU) can be treated effectively by being placed on a low phenylalanine diet. All existing screening programmes of these sorts in the UK must meet criteria set out by the National Screening Committee before their introduction.

Predictive and susceptibility testing

Predictive (pre-symptomatic) testing is used to describe testing of high-penetrance genetic variants, such as Huntington's disease, where a test can give a near categorical diagnosis even in patient's showing no symptoms of disease. In contrast, in many common disorders, such as heart disease and cancer, a combination of genes, behavioural and social/environmental factors (poverty, smoking, exercise, diet) may influence the likelihood of developing an illness. Susceptibility (predispositional) tests for these conditions look for specific genetic markers that are associated with a greater future risk of developing a particular disease. Given the varying impact of environmental factors and the predictive strength of the genetic marker, most susceptibility tests carry a degree of uncertainty about whether a condition will develop, when it will start and how severe it will be (Evans *et al*, 2001). This type of testing is used in conditions more complex than classic monogenic disorders and represents a new and growing class of diagnostic.

Breast cancer is an example of a condition that can be influenced by socio-economic and environmental, as well as genetic factors. Current studies suggest that 3-5% of cases are largely caused by inherited genetic changes, and mutations in the BRCA 1 & 2 genes indicate an increased susceptibility to breast cancer (Miki *et al*, 1994; Wooster *et al*, 1995). However, even in this well-established case it does not mean that a woman will definitely get breast cancer, but that her lifetime risk is significantly increased. Furthermore, there remains considerable debate over the management of women identified as carrying BRCA mutations (see BRCA case study below for further discussion).

Pharmacogenetics

Pharmacogenetics examines the relationship between genetic variation and how an individual responds to a particular medicine. Pre-prescription genetic testing can be used to guide the choice of therapy and dosage levels. This type of genetic testing is discussed in more detail in Chapter 3.

The use of genetic tests in the NHS

The bulk of molecular and cytogenetic genetic testing in the NHS is performed in the 20 Regional Genetics Centres, each serving a population of 2-6 million people. These centres

offer clinical diagnosis, laboratory testing and counselling services for individuals and their families. Other laboratories contribute to this network. For example, some pathology laboratories in haematology departments offer testing for haemoglobinopathies (sickle cell disease and thalassemias), haemophilias, haemochromatosis and Factor V Leiden. The majority of referrals received by the laboratories in the Regional Genetics Centres originate from clinical geneticists, other specialities and primary care staff outside the Centres.

Existing services provide low volume testing and counselling to small, widely dispersed patient groups. However, increased workload, caused partly by the availability of the predictive BRCA 1 & 2 tests, has placed a strain on existing services. In response to the possibility of a future expansion in testing, over £80 million has been invested to strengthen genetic testing services since 2001. Areas of investment include:

- Establishing a UK genetic testing network (UKGTN), to co-ordinate the evaluation, commissioning, funding and prioritising of services for genetic disorders;
- Creating two National Genetics Reference Laboratories to assess new advances and methods of delivery;
- Upgrading laboratory facilities and expanding numbers of specialist staff;
- Funding pilot schemes to examine the benefits of genetics in mainstream clinical areas, such as cancer and heart disease.

As testing services grow and develop there is an increased need to establish best practice and quality assurance policies. In the UK, external quality assessment schemes are in place for some diseases and the majority of genetic laboratories offering clinical testing have official accreditation. The need to have this will be compulsory by 2005.

In general, new genetic tests have come into clinical use in the NHS through the research activities of particular centres rather than in a co-ordinated or uniform fashion, and access to many tests has depended on local expertise and available funding. Part of the rationale for the creation of the UK national Genetic Testing Network (UK GTN) is to ensure greater standardisation of services. This will involve the collection of a master file (the so called 'gene dossier') of information on all genetic tests for inherited conditions to be used in the UK Network, giving details of the tests' characteristics, utility and validity (Department of Health, 2003b). The steering group of the UK GTN, which is a sub-group of the Genetics Commissioning Advisory Group, will then review the information on each file in light of pre-determined criteria. Evaluated tests will then be prioritised to promote tests whose results can impact on the clinical management of the disease involved.

The development of the technology

Historically, it has been cytogenetic methods of testing that have made up the vast majority of services. Subsequently, molecular genetic testing was developed in the mid 1980s in research laboratories where those disease genes mainly involved in rare monogenic conditions were identified. It has been a small step to proceed to testing patients for mutations in these genes (Patton *et al*, 2000). More recently, the sequencing of the human genome has generated large amounts of genetic data and research is now focused on developing a new generation of genetic tests for more common conditions. In particular, progress in this area has depended on the introduction of association genetics, in which large genetic databases are used to find correlations between a disease and a specific genetic marker. A number of new markers have been found that may predict an increased risk of getting conditions such as coronary heart disease.

However, progress in utilising this new knowledge in diagnostics has been much slower than expected. One reason for this is that common disorders are genetically complex and rely on many genes, the variants of which may contribute only a weak effect to the risk of a disease developing. Certain genes may also require interaction with particular environmental factors or with other genes in order to produce an effect. Although the number of new genes associated with diseases or traits has increased steadily from 1993, the strength and certainty with which they can be linked with increased susceptibility to these complex conditions is very different from the robust link in classic single gene diseases. In a review of 268 genes with polymorphisms associated with disease, and in which simple single gene disorders were not included, Hirschhorn *et al* (2002) discovered 166 associations which had been tested for reproducibility of results. Of these only six were repeatable at a high level of consistency. They concluded that the *"current irreproducibility of most studies should raise a loud cautionary alarm"* and that *"clinical applications of genetic associations should not be considered until the degree of certainty far exceeds the level currently achieved for the vast majority of such associations"* (Ibid., 2002 p.60). This lack of reproducibility raises serious questions about the extent to which it will be possible to develop new genetic tests for anything other than a few well characterised sub-sets of diseases such as cancer.

If strong associations can be found, an important recent technical development that will enable genetic testing for common complex conditions is the expansion of DNA microarray or 'gene chip' technology. This technology allows the simultaneous investigation of many different genes. For example, a number of companies are looking to design so-called 'whole genome' scanning arrays. These will enable the entire human genome to be analysed at the same time and provide in-depth analysis of a group of target genes or the study of multiple patterns of gene expression across a variety of tissues. In addition to the increase in the scale of analysis, microarrays also hold the possibility of miniaturising and speeding up laboratory procedures, which were previously time-consuming and slow, and promise to reduce both costs and waiting times.

The development of point-of-care (POC) diagnostic tests, administered in a GP surgery or in a hospital setting, may also greatly enable an expansion of genetic testing. Such devices are already in use and form a rapidly growing $21 billion worldwide market (MarketResearch.com, 2004). However, the great majority of these tests are chemical diagnostics with functions such as blood glucose monitoring, pregnancy testing and the detection of illicit drug use. Some POC diagnostics exist for detecting genetic disease related biomarkers, such as Matritech's NMP22 bladder cancer testing kit (only available in the US). In general, the development of POC genetic testing has been concentrated around technologies that use genetic probes to detect the presence of a large number of DNA sequences in a patient sample. At present these microarrays and DNA chips cannot perform the preanalytical steps needed to prepare the genetic material in tissue samples for testing. Several companies such as Vysis, Aclara Biosciences, Nanogen and Caliper Technologies are working on 'lab-on-a-chip' devices and DNA chip analysers, which can rapidly interpret test results in an attempt to overcome these limitations. In the UK the analytical and diagnostics company LGC has developed assay technology to identify a number of key human genetic polymorphisms, including the Factor V Leiden mutation, which is associated with deep vein thrombosis. These tests can be carried out in approximately 30 minutes and have potential as pharmacogenetic point-of-care tests. However, no such tests are currently available in the NHS.

Potential benefits

Genetic testing provides a number of important benefits. Although therapies are unavailable for many rare genetic conditions, receiving a diagnosis can enable individuals to understand their condition and retain control of their lives. In the case of an adult late onset condition, such as Huntington's disease, diagnosis can inform future lifestyle and reproductive decisions. Similar benefits are also offered by prenatal screening, whilst some forms of neonatal screening can greatly help in the management of a disease. Furthermore, where symptoms suggest a condition, a genetic test can be a non-intrusive method to confirm a diagnosis. For example, a DNA test, as opposed to a painful muscle biopsy, can now be used to confirm diagnosis of muscular dystrophy.

Predictive testing may also be useful if early diagnosis allows interventions or targeted care to reduce suffering or to aid future individual or clinical decision-making. This is the case with people suffering from familial hypercholesterolemia, who can be treated with cholesterol lowering drugs from an early age. In the longer term it is hoped that an expansion of predictive testing services will increase the possibility of early therapeutic intervention, with genetic tests being used to *"identify disease mechanisms, indicate the most appropriate type of therapeutic intervention, and evaluate therapeutic response and disease outcome"* (Bell, 2004 p.453).

2.2 Genetic tests currently in use or under development

Tests for monogenic conditions.

The laboratory-based services that are widely available tend to concentrate almost exclusively on single gene disorders, with the NHS offering some 300 different tests for these conditions. However, the majority of these conditions only affect a very small number of people worldwide and any one test only provides a very limited commercial market. Despite this, when taken together these disorders are thought to affect between 1-5% of the population, representing a significant public health burden, and costing an estimated £2 billion each year to health and social services in the UK (Department of Health, 2003a). As a consequence, there continues to be public sector interest in identifying the genes involved in monogenic conditions and the development of genetic tests, despite the lack of commercial incentives. Many single gene diseases are caused by metabolic or other enzyme deficiencies and a number can now be successfully treated with therapeutic proteins. In general, they are used to confirm diagnosis or assess carrier status, and do not influence the treatment regime for affected patients.

One area where monogenic genetic testing is on the increase is in newborn screening programmes. For example, in August 2005 new legislation in California expanded the State's prenatal genetic screening programme to include 75 hereditary and congenital conditions using tandem mass spectrometry technology (California Department of Health Services, 2005). The technique allows direct chemical analysis of a dried bloodspot taken from a baby, which can detect a variety of genetic disorders such as Phenylketonuria, different varieties of sickle cell disease and Galactosemia. This method is helpful because it can measure small amounts of specific compounds accurately and can test for metabolites, which are not detected by other current screening technologies.

Case study: BRCA genetic testing for breast cancer

In 1994, a research team at the University of Utah working in association with the US firm Myriad Genetics announced they had discovered and sequenced a gene (BRCA1), a mutant form of which caused a predisposition to inherited breast cancer. Myriad applied for a patent on the discovery. A gene patent is not granted on the actual genetic material - which is shared by many people - but on the industrial application to which knowledge of the sequence can be put. In this case the application was for the use of the BRCA gene in laboratory and diagnostic tests and in therapies based on the gene sequence.

During the course of the research it had become clear that a second gene was also closely involved in hereditary breast cancer. Patenting of gene sequences raised serious issues amongst scientists and the public alike. Concerned that Myriad could impose a monopoly on testing if they had patents on both sequences, a UK based group led by researchers at the Institute for Cancer Research (ICR) attempted to find and sequence this second gene. In December 1995, the ICR group announced that they had identified the BRCA2 gene and intended to file for a UK patent. Although the group was against gene patenting they realised that it was the only way of staking a claim on their discovery. That same day, Myriad also announced it had sequenced the BRCA2 gene and also intended to file a patent. The ICR group, funded by Cancer Research UK (CRUK) planned to make the test available free of charge to NHS genetic testing services. In contrast, Myriad preferred all samples to be processed through its own facilities. In 2004 the commercial wing of Cancer Research UK obtained a patent from the European Patent Office for the BRCA2 test in Europe, with the intention that all public laboratories across Europe would be able to use the BRCA2 patent for free. In a further development, in May 2004 the European Patent Office revoked Myriad Genetics' 2001 European patent on BRCA1 *"for diagnosing a predisposition to breast and ovarian cancer"*(Public Health Genetics Unit, 2004*)* after a challenge to the 'novelty' of the invention.

The issues surrounding the development and deployment of BRCA testing highlight some of the social concerns associated with genetic testing, especially where research is funded by public money through charities and universities, and the role of commercial interests in this process. In the US, where direct-to-consumer advertising of medicines and diagnostic tests is allowed, Myriad has been accused of trying to enlarge the potential market for its breast cancer diagnostics through claims they will offer peace of mind to any women who have the test without mentioning specific at-risk groups.

Clinical Issues
As 95% of breast cancer cases are not caused by inherited factors, general genetic population screening is not a realistic prospect. Instead 'at risk' individuals and groups must be identified and offered the option of genetic predisposition testing for BRCA1 and BRCA2. In the UK an estimated 20-50 families per million of the population can be identified as high risk because they have several (usually over four) family members who have developed breast cancer at an early age. Otherwise high risk individuals, who are defined in the latest NICE guidelines as women having a 20% chance of a mutant BRCA gene or with a lifetime risk of greater than 30% of contracting breast cancer, must be identified through family history, relatives with known BRCA mutations and other factors. This effective rationing of test availability is due to economic and service provision constraints. However, public and media misconceptions about the benefits of BRCA testing has encouraged many more women than those that meet the high risk criteria to suspect that they may be at risk. This has led to a significant increase in demand for testing, which can cause psychological distress if suitable information is not forthcoming.

Another difficulty is the interpretation of test results. A negative finding does not mean that an individual is not at any risk of breast cancer, only that they do not have a detectable mutation in either one of the two BRCA genes. They remain at the population level risk of developing breast cancer, adjusted for environment and lifestyle factors. However, a positive test result does mean an individual is at a greater risk of developing breast cancer. Mutations in the BRCA genes are highly penetrant (i.e. they are likely to express an effect), but the exact probability of developing cancer is not 100% and can vary with the particular mutation, as well as being affected by other genetic and lifestyle considerations. Instead the tests allow an estimated lifetime risk of developing hereditary breast cancer. In high-risk families (with multiple affected members) the risk is approximately an 80% chance of developing the cancer by age 70. Without a strong family history of breast cancer, the risk falls to 65% lifetime risk for women with a BRCA1 gene mutation and 45% for women with a BRCA2 mutation. There are also increased risk levels for ovarian cancer associated with a positive test result.

The treatment options for women with a positive BRCA test include an increased programme of surveillance, including self-examination, participation in screening programs such as mammography at an early stage (age 25-35) and possible MRI imaging. Available alternatives include prophylactic surgery – removal of breast or ovarian tissue - and the use of chemopreventative drugs such as Tamoxifen. All of these options are controversial, in part because of the uncertainty involved and a lack of evidence on the relative effectiveness of the treatments. There is some evidence that prophylactic surgery is effective in reducing breast cancer occurrence in women with inherited BRCA mutations, but this reduction is not to zero. Deciding on a course of treatment is therefore a matter of weighing up the risk of developing breast cancer against the risks and benefits of the treatment options. The current medical consensus is that this is a choice ultimately to be made by individual patients assisted by suitable genetic counselling.

In the UK some screening systems already exist and the Government's White Paper on genetics (Department of Health, 2003a) outlined plans to expand these to include cystic fibrosis, sickle cell disease and hearing defect testing for all new-born babies by 2005. As of January 2006, the cystic fibrosis test was available nationally, with the sickle cell disease test due to be made available throughout England and Wales by 2007. The White Paper also raised the possibility of screening all babies at birth to collect a comprehensive record of every genetic marker or indeed their entire genome. This information could potentially be stored on the NHS electronic patient record system currently under development. Although this proposal could have significant health benefits for producing targeted treatments over an individual's lifetime, the government recognised that it also posed significant social and ethical difficulties that would need to be addressed. To this end the Human Genetics Commission (HGC) and the National Screening Committee were asked to conduct an initial investigation into the issue of genetic profiling at birth. The subsequent report reached the following conclusions:

- "Genetic profiling is feasible and likely to become available commercially in less than 20 years.
- Before the offer of universal genetic profiling could be considered at a population level, steps would need to be taken to preclude any misuse of information derived from it.
- Genetic profiling is unlikely to be publicly affordable within 20 years.
- For newborn genetic profiling, issues of consent and the welfare of the child are problematic.

- Genetic profiling may in the future have clinical potential but its effectiveness cannot yet be judged.
- There is a pressing need to develop a programme of research to define the full costs and potential benefits of genetic profiling for the health of children and adults.
- Genetic profiling cannot be applied as an NHS screening programme in the near future. The topic should be kept under review and be revisited in five years." (HGC and National Screening Committee, 2005, p.7)

Tests for common conditions.

As mentioned above and shown in Table 2.1, only a small number of DNA tests are currently available for common conditions, and these tend to focus on defined subsets of diseases caused by one or two inherited genes e.g. BRCA. In this sense, they are very like tests for classic monogenic disorders and to date only the APO E4 test for increased susceptibility to Alzheimer's disease can be thought of as being significantly different from a rare inherited sub-set of a common condition. One of the major attractions of predictive testing is that it offers the possibility of pre-emptive treatment, which would represent an important change in existing medical practice. Unfortunately, at present there is little that can be done to prevent conditions such as Alzheimer's and this raises major ethical questions about the benefits of testing (see case study below). Even in cases with some possibility of treatment, such as hereditary breast cancer, the options are still limited and have significant side effects.

Table 2.2 gives details of a number of predictive genetic tests that are in development for common, serious conditions including forms of heart disease, diabetes, osteoporosis and depression. These are based on reports identifying specific genetic markers associated with particular conditions. However, a stronger evidence base on the predictive strength of genetic markers in these diseases may be needed before they are widely used and some remain controversial (e.g. depression). This may not be easy, as there is uncertainty about how to design such studies so that they give meaningful, replicable results. Furthermore, it is increasingly recognised that translating this knowledge into routinely applied diagnostics will be a challenge, and that large-scale studies are needed to determine which genetic factors are clinically relevant. Estimates for both the number and timescale of fully validated predictive tests for common conditions vary widely, with some commentators increasingly questioning whether many will ever reach the market.

Tests for infectious diseases.

There is a growing trend towards using genetic tests to detect viral and bacterial DNA in order to more accurately diagnose infection and a number of firms are pursuing this strategy with some success. Many of these tests are confirmatory – that is they aid the detection of infectious agents, although in some cases identification of a particular viral genotype can affect the treatment of the disease. There are six major strains of the Hepatitis C virus (HepC), distinguished by different genotypes. Current NICE guidelines recommend that patients with HepC genotypes 2 and 3 receive a 24 week regimen of treatment with Interferon alpha and Ribavarin, whereas patients infected with other genotypes of the virus benefit from an extended (48 week) course of drug therapy. Other instances where viral genotyping can affect the course of treatment include human papillomavirus infection (Molijn *et al*, 2005), HIV/AIDS (Phillips, Veenstra and Sadee, 2000) and potentially Hepatitis B infections (Verschuere, Yap and Fevery, 2005) (see Chapter 3 for further discussion of this issue).

Tests for somatic mutations.

Unlike the genetic changes (inherited 'germline' mutations) discussed above, somatic mutations arise spontaneously in particular tissues of an individual and are not inherited. The most common example of somatic mutations are those which cause non-inherited forms of cancer. These genetic changes can be caused by environmental damage, such as radiation and smoking. For example, the UroVysion test (see Table 2.1 below) is used to detect mutations in bladder cells in individuals who have already been diagnosed with bladder cancer and have had a tumour removed. The test checks for cells with unusual numbers of chromosomes (aneuploidy) which would indicate that mutant cells remain in the tissue and could give rise to further tumours. This test is essentially a surveillance mechanism. A second genetic test for somatic mutations, Pre-Gen Plus, is designed to look for genetically abnormal cells in individuals who are at high risk of developing colorectal cancer. It is important to note that somatic mutations are not inherited or passed on, and exist only in cancerous or pre-cancerous cells in the body and not in the cells of other tissues. This means that the genetic tests must focus directly on samples from the affected tissue, as the abnormalities may not show up in blood tests.

Table 2.1 Examples of established commercial genetic testing kits and laboratory services

Test	Disease	Company	Applications
Monogenic conditions			
INNO-LiPa CFTR	Cystic fibrosis	Innogenetics NV	Confirmatory diagnosis. DNA test for a range of mutations in the CFTR gene, which cause cystic fibrosis. Carrier screening also available.
N/A	Thrombophilia	Roche Diagnostics	Aid clinical management. Tests for gene mutations that cause inherited thrombophilia which can predispose individuals to certain cardiovascular conditions.
Common conditions			
INNO-LiPa APOE	Alzheimer's Disease / Risk analysis	Innogenetics NV	Predictive testing. The ApoE4 variant of the ApoE gene is a known indicator for types of Alzheimer's disease and is also linked to heart disease risk.
BRAC-Analysis	Breast & Ovarian Cancer	Myriad Genetics	Predictive Testing. Detects mutations in the BRCA1 and BRCA2 genes, which increase susceptibility to hereditary breast and ovarian cancer.
MELARIS	Melanoma	Myriad Genetics	Predictive testing. Tests for gene mutations which indicate inherited susceptibility to melanoma (skin cancer).
Infectious diseases			
HPV test	Cervical Cancer	DiGene	Screening. Detects the presence of human papilla virus (HPV) DNA. HPV is one of the most common causes of cervical cancer. The disease is almost always preventable if detected in pre-cancerous stages.
Somatic mutations			
UroVysion	Bladder Cancer	Vysis	Screening/risk analysis. Detects chromosomal abnormalities associated with recurring bladder cancer.
PreGen-Plus	Colon Cancer	Exact Sciences	Screening/early detection. Analyses mutations associated with colon and rectal cancer and pre-cancerous conditions to inform future treatment.

Table 2.2 Selected commercial genetic tests for common conditions currently in development

Test	Disease	Company	Application	Stage of development
Interleukin-1 (IL-1) mutations	Coronary Heart Disease (CAD)	Interleukin Genetics	Predictive testing. Testing for variants of the IL-1 gene, associated with increased risk of coronary artery disease (CAD).	Two clinical trials have evaluated the association of the IL-1 marker with traditional CAD risk factors such as smoking and with evidence of arteriosclerosis.
HOB1 gene	Obesity, Diabetes	Myriad Genetics	Predictive testing. Evaluate risk of adult-onset diabetes.	Development stage unclear.
DEP1 gene	Depression	Myriad Genetics	Gene believed to be involved in depression, acts in a pathway independent of SSRI's and may provide a predictive or pharmacogenetic test.	Development stage unclear.
BMP2 gene	Osteoporosis	deCODE Genetics	Identification of three variants of the gene which gives increased risk of developing osteoporosis	The relevant gene has been isolated, the markers optimised and the test is now in product development.

2.3   What are biomarkers?

The United States National Institutes of Health (NIH) recently defined a biomarker as *"a characteristic that is objectively measured and evaluated as an indicator of a normal biological process, pathogenic process or pharmacological responses to a pharmaceutical intervention"* (Naylor, 2003 p.525). Biomarkers are often by-products of the body's metabolism and natural functions. Molecular diagnostic tests measure biomarkers in order to indicate healthy or abnormal levels of biological activity in the body. For example, cancerous cells often express unique proteins, or over-express common ones, on their surface. Neurodegenerative conditions like Alzheimer's disease can produce abnormal proteins as part of their pathology, some of which can be detected in the spinal fluid (see case study below). Some blood (serum) biomarkers are produced as cell surface markers by a range of tissues, organs or tumours. When detected in abnormal amounts, each of these different biomarkers can be used to indicate disease.

Most biomarkers are proteins, but they can also be other molecules such as fats or antibodies. For example, cholesterol levels in the blood are measured as an indicator of coronary and vascular health – high cholesterol can suggest a high fat intake and increased risk of arteries becoming blocked. The specific binding of methyl groups onto DNA (known as methylation tagging) is also used as a biomarker. Methylation of a gene can cause it to be inactivated and these tagging patterns are increasingly being used as biomarkers for the early detection of cancer.

Under the definition above, genes can be described as biomarkers, with different forms (alleles) of a particular gene indicating the likelihood (or occasional certainty) of a particular disease state developing, or indicating that an individual has a particular subtype of a condition. However, molecular biomarkers are generally distinguished from genetic tests. While some biomarkers can be derived from genetic testing models, for example assessing the activity of a particular gene by measuring the levels of a protein it codes for, other molecular biomarkers are unrelated to genetic factors. As a consequence, biomarkers can report on conditions caused by a complex pattern of gene, environmental and behavioural interaction, and can be developed even when the specific cause of a disease is unknown.

The development of the technology

Progress in the discovery and development of molecular biomarkers has been greatly facilitated by the rise of proteomics, a new science that focuses on studying the role, structures, localisation, and interaction of proteins. New technologies such as protein chips and new uses for older technologies such a mass spectrometry allow broader and more in depth analysis of expressed proteins in tissues, including those carried in the blood. The analysis of gene expression on its own provides limited information about protein-protein interactions and the internal state of cells. Proteins, once expressed, are modified and interact with many other cellular factors, and are more closely involved in the cause of pathological states and phenotypic (observable) symptoms than genes. Proteomic analysis of disease may therefore produce more accurate biomarkers than either those currently available or those derived from genetic analysis (Petricoin *et al*, 2004).

Microarrays can also perform complex parallel analysis of protein expression and have been useful in discovering new biomarkers. They may also be used to validate biomarkers in a diagnostic or predictive context by analysing and correlating sets of markers with a particular condition or clinical state.

Potential benefits

Biomarkers can either be used as molecular diagnostics, aiding or possibly replacing existing clinical diagnostic methods, or they can provide predictive risk assessment. They can be subdivided into three categories (Frank & Hargreaves, 2003), which indicate the different benefits offered:

Type zero biomarkers.
These correlate with the natural progression of a disease over time, and can be linked to particular clinical states. For example, rising levels of PSA (prostate specific antigen) can indicate incidence of prostate cancer. A number of biomarkers are being developed which are predictive of a future illness, can identify early onset diseases and measure the efficacy or toxicity of a particular therapy.

Type one biomarkers.
These indicate the effect or change caused by a therapeutic intervention, such as a drug, and are used by the pharmaceutical industry to inform and monitor drug development.

Type two biomarkers.
These are considered 'surrogate endpoint markers' which indicate a state of health reflecting clinical benefit. They are generally used in clinical trials to replace clinical endpoints – i.e. they show if a patient appears to be getting better within the limited time-span of a trial or experiment. Biotechnology companies looking for new ways of detecting disease also use type two biomarkers.

It is the diagnostic applications primarily associated with type zero biomarkers, which are relevant to this report, especially their potential in predictive testing for common conditions.

2.4   Protein biomarkers currently in use or under development

Genetic tests are predominately used for monogenic disorders, while protein biomarker research has focused on more complex and more common conditions such as Alzheimer's, heart disease and cancer.

At present, relatively few tests are on the market (See Table 2.3.). The Tau, phosphorylated Tau and beta-amyloid proteins are biomarkers that are associated with Alzheimer's disease. Tau is a stabilising protein found in neurons, which becomes abnormally phosphorylated and forms long filaments in the course of Alzheimer's progression. This action has the effect of causing neurons (brain cells) to malfunction. Although Tau is normally an intracellular protein it is often released into the cerebro-spinal fluid (CSF) due to the increased rates of cell degeneration that occur with Alzheimer's Disease and a monoclonal antibody assay for Tau/phospho Tau in the CSF can detect these increases. A similar test is used for beta-amyloid protein, which is the main component of the senile plaques, which are one of the most widely recognised pathological features of Alzheimer's. As neither of these biomarker tests are 100% specific to Alzheimer's disease, it is recommended that both tests should be used in conjunction to assist in diagnosis. This is an example of a testing model where biomarkers are combined to increase their utility and accuracy both in detecting disease and in differentiating between similar diseases. Current Alzheimer's diagnosis relies on clinical evaluation, elimination of other possible causes of the symptoms (of which there are several, including normal age-related memory loss) and ultimately confirmatory diagnosis by post mortem examination. As a consequence, there is a market for biomarker diagnostics that

could assist and simplify this process. However, confirmatory diagnostic tests do not alter the limited clinical treatment available for Alzheimer's disease.

Increases or decreases in methylation patterns are common in most human cancers. Companies such as Epigenomics and MethylGene, are investigating the possibilities for reading the methylation patterns of cells or specific genes as markers to indicate cancerous or pre-cancerous states of disease progression. Developmental diseases, such as Angelman's and Prader-Willi syndromes, have already been associated with methylation changes and in Fragile X syndrome the mutated FMR1 gene is methylated.

Although other biomarker tests are largely diagnostic, the Prostate Specific Antigen (PSA) test is used in conjunction with a physical examination to screen for risk of prostate cancer in men. PSA is a protein produced by the prostate gland, which can be detected in the blood. Increased PSA levels are often indicative of an inflamed prostate, which in turn, may indicate the presence of a prostate tumour. However, there are difficulties with the accuracy of this test, as there are a number of benign factors which can also cause an enlarged prostate and the test produces an elevated rate of false positive diagnoses. Caution is also needed when testing for carcinoembryonic antigen (CEA), another tumour biomarker. CEA is elevated in patients with colorectal, breast, lung, or pancreatic cancer; however increases in CEA can also be caused by other factors, such as smoking. Despite this, CEA testing post-surgery for colon cancer is an effective way of determining the adequacy of postoperative therapy.

The future development of biomarkers

New biomarker discovery technologies, developed by companies like Metabometrix and Ciphergen, offer possibilities and directions for the future development of these diagnostic markers. Both companies espouse the idea that future biomarker tests will consist of multiple marker analysis to better reflect the pathology of disease and offer improved predictive power. Metabometrix aims to look at a broad biochemical analysis of tissues and fluids (systems biology) over time to provide a molecular profile of disease and identify biomarkers. Ciphergen plans to focus on multiple protein expression profiling (proteomics). Both these approaches mark a move towards a genuine analysis of common complex conditions. It may be that biomarkers have the potential to provide the next level of diagnostic and predictive testing, as compared to genetic testing which has predominately focused on single target analysis of simple conditions or subsets of complex ones. Advocates argue that regular protein profiling may be used to give prognostic information and follow the progress of disease, with initial diagnosis being done by genetic tests.

In the future, tests that offer early diagnosis may allow some scope for preventative measures to be taken and this would have the potential to alter current medical practice. A number of pharmacogenetic tests are also in development to identify patients who are particularly susceptible or likely non-responders to particular cancer therapies (both targeted drugs and chemotherapy). If successful, these tests could act in a similar way to the HER2 gene test to expand the targeting of drugs to specific patient groups (see Chapter 3).

Table 2.3 Selected biomarker tests on the market

Test	Disease	Company	Application
NMP22	Bladder cancer	Matritech	Non-invasive test for bladder cancer marker proteins. Also identifies risk of recurrence.
PLAC test	Coronary heart disease (CHD)	DiaDexus	Measures levels of a blood protein Lp-PLA2, which is a risk factor for CHD independent of cholesterol levels.
Innotest hTau Ag /Innotest β-Amyloid	Alzheimer's disease	Innogenics NV	Measure the level of two marker proteins Tau and Aβ42 linked to the presence of Alzheimer's related structures in the brain.

Table 2.4 Biomarker products in development

Test	Disease	Company	Application	Development stage
Early detection and classification tests.	Prostate, breast cancer.	Epigenomics	Detects pattern of gene methylation in various cancers.	Clinical marker validation
Pharmacodiagnostic tests used with Roche's anticancer drugs.	Colon, prostate, and breast cancer.	Epigenomics	Detects pattern of gene methylation in various cancers.	Clinical marker validation – colon cancer test moving into kit development in 2006. Licensed to Roche Diagnostics in 2003.
Biomarker assays for cancers	Prostate, breast and colon cancer	Oncomethylome	Detects for methylation patterns in tumours for early diagnosis.	In early clinical development
Pharmacodiagnostic test for chemotherapy response.	Brain tumours.	Oncomethylome	Measures resistance or susceptibility to chemotherapy drugs.	In early clinical development
NMP48, NMP66 and NMP35	Prostate, breast, and colon cancer.	Matritech	Protein-based blood sample diagnostic test.	Clinical trials underway to investigate protein utility.

Case study: Biomarkers, genetic variants and Alzheimer's disease

Alzheimer's disease is a progressive neurological disease and one of the most common causes of dementia – deterioration of memory and other mental faculties. Population lifetime risk of developing the disease is 10-12% and the average age of onset is 80-85. (PHGU, 2004b) A rare familial early onset form, where the average age of onset is 60, accounts for 5% of cases. This condition is caused by inherited mutations in one of a set of genes known as APP, PSEN1 and PSEN2 (PHGU, 2004b).

In the more common late-onset Alzheimer's disease, a family history can also be inferred in 10-25% of cases. Studies have found a link between variants of a blood protein apolipoprotein E (ApoE) and Alzheimer's (American College of Medical Genetics/ American Society of Human Genetics Working Group, 1995). There are three variants of the ApoE protein, coded for by three variants (alleles) of the APOE gene (APOE2, APOE3 and APOE4). The APOE4 variant is associated with a higher risk of Alzheimer's disease (PHGU, 2004b). Genotyping studies have shown that Alzheimer's sufferers are three times more likely to have a copy of the APOE4 gene than unaffected people in control groups. Between 34-65% of patients carry the APOE4 allele, but it is also present in 24-31% of unaffected individuals (ACMG/ASHG Working Group, 1995). Therefore, while there is a definite association between APOE4 and Alzheimer's, it is not strong enough for predictive or diagnostic clinical testing, as neither a positive nor negative test for the APOE4 allele is conclusive. It has been suggested that the risk of developing APOE4 associated Alzheimer's is influenced by other risk factors such as age, gender, ethnicity, smoking and a high fat diet (PHGU, 2004b). Currently, the model of APOE4 action is not fully understood, although in the future it may be useful in evaluating risk in conjunction with other risk factors and biomarkers.

Drugs such as donepezil (Aricept) and galantamine (Reminyl) are available to treat the mild to moderate symptoms of Alzheimer's, and memantine hydrochloride (Ebixa) is able to slow the progression of symptoms in later stages, but they cannot halt the disease, which is invariably fatal (Ibid.). As a consequence, early identification and predictive testing for Alzheimer's disease is an ethically controversial subject, and there are concerns that there is little value in early identification of sufferers, especially as the information is likely to cause distress and anxiety to those receiving it. APOE4 may also be a predictive factor for cardiovascular disease, prompting concerns that patients may discover unwanted information on Alzheimer's risk while participating in heart disease research. Despite serious scientific criticism of its predictive value, APOE genetic tests are available from some genetic testing laboratories and there are anxieties about their premature use as a result of commercial involvement in genetic testing. In the UK, genetic testing for Alzheimer's disease is only used in early onset familial cases and only involves testing for the APP and PSEN gene variants (PHGU, 2004b).

2.5 Protein biomarkers and genetic tests: clinical use and practice issues

Biomarker analysis and genetic testing can be delivered in a number of formats:

Proprietary laboratory tests - involve a small number of accredited clinical laboratories, which invest in the required equipment, quality assurance processes and personnel to carry out a specialised and specific testing procedure. They may in-license a specific procedure from a biotechnology or diagnostics company, or the laboratory may develop and provide in-house analysis services, such as those offered by many NHS testing laboratories. Provision of

a laboratory test may also be a good way of familiarising the scientific and medical community with the existence and providence of a test before launching a kit version.

Lab test kits and automated lab tests - are sold to a wider number of clinical laboratories and contain all the materials needed to carry out a specific test, which can be performed upon a GP's request and the supply of a patient sample. The lab will then process the sample and provide the results often with a written report that can help the doctor interpret the findings. Lab test kits are often derived from successful proprietary lab tests.

Point-of-care test devices - are mainly sold for use in medical facilities or a doctor's office. They can be used by personnel who are not accredited or trained to perform laboratory tests and are similar to pregnancy tests, although they are not for patient self-administration.

Direct-to-consumer tests - some companies are offering direct-to-consumer testing services, which involve sending biological samples (hair, saliva) through the post. This is then analysed by a centralised laboratory.

With the possibility of future testing expanding beyond rare monogenic disorders there are various organisational issues that will need to be addressed. Routine predictive testing for common diseases would involve large patient numbers and place heavy demands on the existing health service infrastructure. In addition, as tests begin to focus on conditions involving complex gene/gene and gene/environment interactions, sophisticated technologies and well-trained specialist staff will be needed to interpret test results. The prospect of using genetic testing techniques in molecular pathology also raises questions regarding the most effective division of labour between clinical genetics and pathology laboratories. The expanding role of genetics is in contrast to the limited number of genetic counsellors. Staff across the NHS may need to be trained to identify patients for whom testing is relevant and to communicate information about genetic risk. Finally, relatively little work has looked at the cost effectiveness of genetic testing (Carlson *et al*, 2005) and new methods of measuring the potential benefits of genetic testing need to be developed. Further economic evaluation must go beyond the limited number of health technology assessments that have been completed, and account for the impact of such services upon the individual, the family and society, and establish both the value of the services to these groups and the most effective means of delivery (Griffith *et al*, 2004).

2.6 Ethical, legal and social issues raised by protein biomarkers and genetic tests

The increased use of genetic testing and molecular biomarkers raises a series of important ethical, legal and social issues, although the extent to which these are novel is much debated. Some have argued that the information yielded from some forms of genetic testing is unique, as it is able to help predict an individual's future health status. As a consequence, providing test results that have implications for kin and may result in stigma and psychological distress, justifies tight governance with respect to informed consent and privacy. In contrast, others have argued that the widespread perception of genetic tests based on rare disorders such as Huntington's, where the presence of the 'faulty' gene variant carries a high likelihood of developing the disease, is misleading. This is not only the case for common multifactorial diseases, where many different genes and environmental factors contribute to pathology, but also for many monogenic disorders where clinical symptoms vary considerably between individuals. As Melzer and Zimmern (2002) argue:

> *Outside the high penetrance, single gene disorders, genetic tests, like most other medical tests, provide evidence only of statistical risks ...there is little to suggest that they will have any greater clinical value than the more conventional physiological risk markers, such as blood pressure or cholesterol concentrations.* (Ibid., p.863)

This position can be seen, for example, in the US approach to using genetic test results in assessing insurance premiums, where it is treated just like any other medical information.

Privacy and confidentiality

Doctors have a duty of confidentiality to their patients not to reveal any information collected or uncovered during the course of a medical examination or treatment, without obtaining the patient's prior consent. Information revealed by genetic testing creates new difficulties in that it may relate to individuals other than the person tested. Genetic research on particular illnesses often involves the study of inheritance, as exemplified by the use of family pedigrees. These have been used to identify the genes involved in many rare conditions, which then allow the development of diagnostics. A positive test identifying an individual as carrying a gene for a dominant late-onset disorder may also identify the parent from whom the gene was inherited and who may not be aware they will end up suffering from the disease. Similarly, a test that reveals that an individual carries a recessive gene for a particular condition could mean their siblings are also at risk of being carriers and could potentially pass the gene on to their offspring (Pilnick, 2002). Dilemmas therefore occur over whether or not to reveal this information to the affected parties who have not chosen to take a test and may not be aware of any increased risk. The doctor's duty to confidentiality is not absolute and can be superseded if the failure to release information could result in significant harm to another individual or the public (Melzer and Zimmern, 2002). At present the preferred approach is to encourage voluntary disclosure or permission to disclose by the patient. However, this system does assume an idealised set of clear and open family relations, with good communication between all family members, something that is not always the case.

Genetic information, insurance and employment

A survey by the Human Genetics Commission (HGC) found widespread concerns amongst the British public that employers and insurance companies may gain access to and misuse personal genetic information (Human Genetics Commission, 2001). Insurance companies and employers may both have reasons for wanting to make use of knowledge from genetic tests. In the US, results of genetic tests are already used in some cases to set insurance premiums, including those for health insurance. A commonly raised fear is that widespread use of genetic information could lead to an uninsurable genetic "underclass" (Morrison, 1998). In the UK a moratorium on using or requesting information from genetic tests in almost all forms of insurance has been in place since 2001, and was originally intended to expire in 2006. In March 2005 the Government issued a 'Concordat and Moratorium on Genetics and Insurance' developed in conjunction with the HGC, Genetics and Insurance Committee (GAIC), and the Association of British Insurers, which extended the moratorium on predictive genetic tests until November 2011 (Department of Health & Association of British Insurers, 2005). Unlike many other countries, it is not illegal in the UK to discriminate between individuals for insurance purposes on the grounds of medical information, provided the information is reliable enough. The terms of the 2005 concordat allow information from diagnostic genetic tests to be utilised, subject to customers' consent. Prior to the initial moratorium, the Genetics and Insurance Committee (GAIC) was responsible for evaluating genetic tests to see which were sufficiently accurate to be used in setting insurance premiums and provision is made under the concordat for the committee to resume this role after the

moratorium expires. A genetic test for Huntington's disease was approved by GAIC for use in life insurance in 2000 (Pilnick, 2002). It is worth noting that this debate only concerns available tests for relatively rare monogenic disorders (Low, King and Wilkie, 1998), and the number of people affected by even the most common of these (such as cystic fibrosis) will be small. Furthermore, there may not be as great an effect on insuring these individuals as some commentators have suggested. In particular, the existence of the National Health Service is likely to reduce much of the potential impact of using genetic information, compared to the insurance-based US healthcare system.

It has also been suggested that employers may want to use genetic testing to screen out potential job applicants who are at increased risk of developing an occupational disease for which they are genetically predisposed. In the US, employers are prevented from doing this through the use of disability legislation. In contrast, UK law defines disability only in terms of conditions present at the time of application (Ibid.) and would not prevent this practice. Despite this, there is little evidence to date that employers are interested in pre-employment genetic screening in the UK.

Informed consent and the consequences of testing

It is a widely accepted principle in medicine that patients must give their informed consent before any intervention is carried out. Once the patient is judged mentally competent the healthcare professional must also make sure that the patient has sufficient information available and a clear understanding of the proposed action in order to make the decision. There has been discussion as to whether lay knowledge of genetics is sufficient to meet these criteria for informed decision making about genetic tests. One particular issue concerns patients' comprehension of the range of consequences that might follow from a diagnostic result. A genetic test could allow a doctor to better evaluate a patient's condition and enable decisions to be made about the most appropriate course of further treatment. However, in addition to the possibility of uncovering information on other family members as discussed above, a positive test result for a genetic condition such as Huntington's can lead individuals to feel depressed and socially stigmatised. It could also have a negative economic impact through failure to get life or health insurance, or through loss of employment (Levitt, 1999). The difficulty of fully assessing the particular benefits and costs of undertaking a genetic test may be further compounded by the doctrine of non-directive genetic counselling. Although non-directive counselling allays fears about coercion and eugenics, it also means that patients must rely on their own, often limited, knowledge of the issues involved in order to raise particular concerns about the broader consequences of taking a test for access to insurance and employment.

Another potential consequence of a positive test result is accepting the implied responsibility that goes with it. In 2003 a Labour party policy document proposed an option that patients could enter into a 'lifestyle contract' with their doctors, which would guarantee them a certain level of service provision, but would also outline their responsibilities to stop smoking, improve their diet or take more regular exercise. The first generation of genetic tests, such as for Huntington's, have been predictive for largely untreatable diseases, but genes have now been isolated that are associated with potentially preventable diseases, such as heart disease and cancer, and with increased risk from smoking and obesity (Marteau and Lerman, 2001). This opens up the possibility that people receiving positive genetic test results for increased susceptibility factors for a particular disease will also be obliged to change their behaviour in order to manage their increased risk. However, as Marteau and Lerman note: *"telling people that they are at risk of developing a disease is rarely sufficient to change behaviour"* (Ibid., p.1056) and other research has shown that people's financial

status and their work and family responsibilities are important factors in their ability to lead a 'healthy lifestyle' (Levitt, 1999). The proposals mentioned above generated significant political and media opposition amid fears that patients would be compelled to make the recommended changes under the threat that treatment would be withheld. It therefore remains to be seen if knowledge of an increased genetic risk compels individuals to take greater moral responsibility to act differently.

The governance of genetic testing

The regulation of genetic testing in the UK has historically been left to professional governance arrangements and the non-statutory advisory system based on the working of the Advisory Committee on Genetic Testing (ACGT). Until recently, this system has worked effectively, ensuring that testing for most important monogenic conditions was linked to genetic counselling and that services were always accessed through a medical practitioner. However, the emergence of commercial genetic testing services sold direct to the public has led to calls for more statutory oversight. In its report *Genes Direct* (2003) the Human Genetics Commission recommended that there should be some independent mechanism to consider the scientific and clinical validity and utility of any genetic testing service, and that all commercial genetic testing services should be subject to pre-marketing regulatory review. As of January 2006, these recommendations had not been acted on by the UK government and there are currently no legal requirements that control the predictive validity of a test or its clinical utility (Hogarth, Melzer and Zimmern, 2005). However, the European Union's In Vitro Diagnostics Directive, which was passed in 2003, deals with issues concerning the safety, quality and accuracy of genetic testing (see Section 5.5 below)

2.7   Realising the potential of new molecular diagnostics

To date, both cytogenetic and molecular methods of genetic testing have predominately been used to confirm diagnosis of a large number of individually rare, 'simple' single gene disorders. A small range of tests has also been available to assess the health status of a foetus or newborn child (prenatal/neonatal screening), or to detect genetic changes in healthy individuals that may have implications for other relatives (carrier testing). These tests have been expanding slowly and make up the vast majority of the ~300 molecular genetic tests currently offered through the NHS. A range of conditions are covered, from cystic fibrosis, involving an estimated 15,000 tests per year (NHS, 2003), to a plethora of conditions for which less than one test per year may be required, and services have evolved accordingly. The network of Regional Genetics Centres enables low volume laboratory testing, clinical diagnosis and counselling services to be provided to widely dispersed patient groups and their families. Commercially available testing services and kits have concentrated almost exclusively on a similar selection of diseases, which represent a very limited market.

However, following the sequencing of the human genome and the possibility of identifying genetic factors involved in more common conditions, there were high expectations that genetic testing services were set to expand dramatically. For example, it was proclaimed in 1998 that *"it would be surprising if most of the major genetic factors involved in human disease were not defined in the next 5-10 years"* (Bell, 1998 p.618). This would lead to a series of new genetic tests that could be applied to a wide range of conditions, including the evaluation of a patient's risk of developing a disease, and would have a profound clinical impact. Such tests would increase the possibility of early therapeutic intervention and targeted clinical management. In addition, proteomics was also heralded as having the potential to facilitate a new era of biomarker discovery, which might provide the next level of diagnostic and predictive testing.

In response to these expectations, the UK government has invested heavily in strengthening existing genetic services and in preparation for future expansion. Likewise, the prospect of larger markets has seen the medical diagnostics industry begin to start the development of a number of tests for common conditions. However, whilst the potential of some of these tests is significant, there are a series of major challenges that will need to be overcome before the widespread provision of this new range of diagnostics becomes a reality. Chief amongst these is the need to establish clinically validated associations between a genetic or biochemical marker and a disease state and evidence of economic 'added value'. The inability to replicate some of the initial findings from completed gene-disease association studies has generated scepticism about the value of existing approaches for detecting genetic variants linked to common conditions such as heart disease and cancer (Colhoun, 2003).

Evaluating the clinical utility of genetic and protein based diagnostics is also more problematic for tests for complex disorders, which are likely to vary in their predictive value, their potential to direct prevention or treatment efforts, and their personal and social consequences (Burke *et al*, 2002). As a result, there may be a need for formalised assessment of all new tests before they are introduced into routine clinical practice.

Furthermore, any new tests that are introduced will place further pressure on existing laboratory and genetic counselling services. Whether all genetic tests will require similar pre- and post-test counselling is unclear and will depend on the implications for patients of the information created by the test. However, if an expansion of testing enables risk assessments of the likelihood of future disease, it is important that staff training and education evolves to incorporate the necessary skills required to interpret and communicate this information. Surveys of public opinions on advances in genetics have consistently shown that confidentiality and consent to the use of genetic information are key issues.

As a consequence of these important barriers to innovation, the high hopes that followed the euphoria of sequencing the human genome have been replaced by a much more cautious view on the prospects for genetic testing and protein based biomarkers in recent years. It is now generally acknowledged that the development of valid, clinically useful tests for common conditions will take far longer than many people initially predicted. In the short term at least, it appears that genetic testing will provide benefits by allowing the characterisation of some diseases at the molecular level, predominantly aiding medical research rather than clinical diagnosis (Bell, 2004).

Chapter 3. The discovery and development of new small molecule drugs and the possibility of 'personalised' medicine

3.1 The productivity crisis in the pharmaceutical industry

Historically the process of pharmaceutical development has focused on producing drugs for large groups of patients to treat specific disease conditions. These drugs have generally been small organic chemical entities produced by medicinal chemistry and usually referred to as 'small molecule' drugs. The resulting pharmaceuticals are tolerably safe for the majority of users, although they often vary somewhat in effectiveness (Moos and Steliou, 2000).

In the last 50 years pharmaceutical companies have produced a steady stream of new medicines. However, more recently the industry has suffered from an ongoing crisis in both innovation and productivity in discovering and developing new drugs (Horrobin, 2000; Kraft, 2004). As well as internal unease over the lack of new products coming through drug company 'pipelines', there are concerns from charities and other bodies that not enough is being done to produce new medicines for some serious conditions, such as cancer, as well as the most common diseases in the developing world (Goodman, 2000; Schieppati, Remuzzi and Garattini, 2001). A major reason for this productivity crisis is that in the last 20 years the financial cost of the drug discovery and development process has greatly increased. As a consequence, research and development spending by pharmaceutical companies has risen sharply. However, in the same period the time taken to bring a new drug from discovery to the market has doubled, and now stands at 12-15 years (Kelly, 2002; Wardell and Sheck, 1983). Furthermore, the number of new drugs reaching the worldwide market has been falling since the 1960s (Horrobin, 2000).

Table 3.1 Falling levels of New Molecular Entities and Biologics Licence Applications
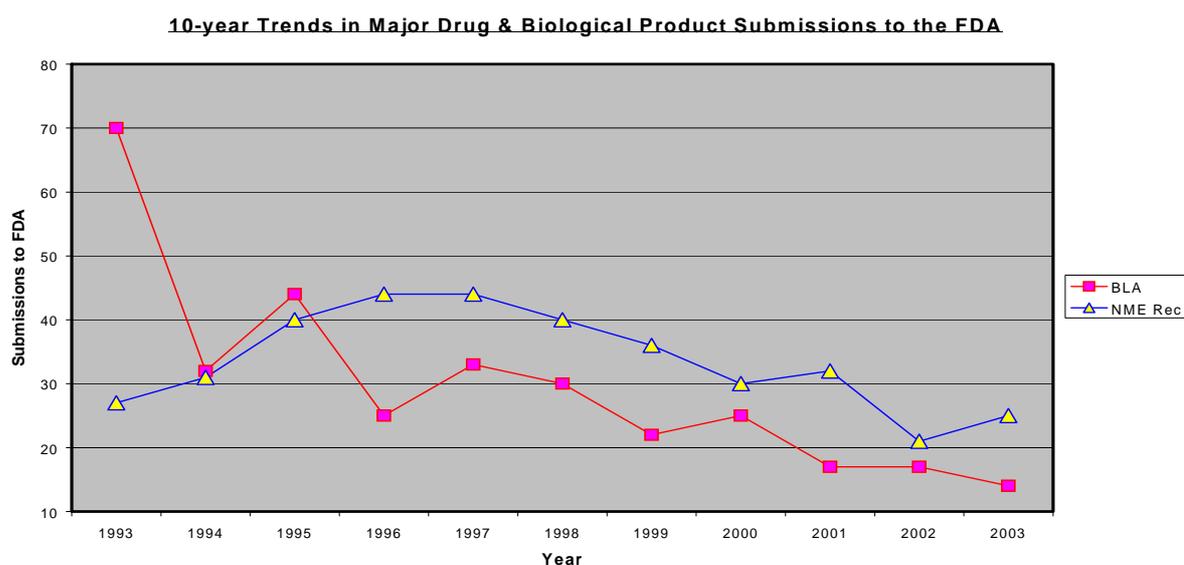
Put simply, it is taking increasing amounts of time and money to produce fewer new drugs than ever before. This situation led the US Food and Drugs Administration to publish a White Paper *'Innovation or Stagnation'* in 2004 on the productivity crisis in which it noted:

"Today's revolution in biomedical science has raised new hope for the prevention, treatment, and cure of serious illnesses. However, there is growing concern that many of the new basic science discoveries made in recent years may not quickly yield more effective, more affordable, and safe medical products for patients. This is because the current medical product development path is becoming increasingly challenging, inefficient, and costly. During the last several years, the number of new drug and biologic applications submitted to FDA has declined significantly; the number of innovative medical device applications has also decreased. In contrast, the costs of product development have soared over the last decade. Because of rising costs, innovators often concentrate their efforts on products with potentially high market return. Developing products targeted for important public health needs (e.g., counterterrorism), less common diseases, prevalent third world diseases, prevention indications, or individualized therapy is becoming increasingly challenging. ... If the costs and difficulties of medical product development continue to grow, innovation will continue to stagnate or decline, and the biomedical revolution may not deliver on its promise of better health." From FDA (2004a) executive summary http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html

The process of drug discovery can be considered as occurring in two stages. The first stage is pre-clinical and concerns the search for compounds that have pharmacological activity against a selected biological target[1] and have suitable drug-like profiles in terms of uptake, elimination and toxicity in the body. Compounds that are successful in this phase (which includes the process of testing in animal models) then go on to the clinical trials phase where over time they are tested for safety and efficacy in increasingly larger groups of human volunteers and patients. This second stage takes much longer and is significantly more expensive than the pre-clinical development stage. However, the attrition rate for new compounds is high at all stages of the development process, with the great majority of compounds entering pre-clinical development failing to reach the market (Ibid.). Estimated attrition rates suggest that as few as one in 5000 new compounds entering pre-clinical development will reach the market (Kelly, 2002) and up to 50% of drug candidates do not make it through clinical trials (Kraft, 2004). This makes the process of drug innovation an extremely risky one, and pharmaceutical companies have adopted a number of strategies and practices to reduce the risk of failure and the associated financial losses.

For example, rather than investigating entirely novel types of potential drugs, much pharmaceutical research focuses on a limited group of drug targets and drug formulae in specific markets - such as anti-hypertensives - which have a tried and tested track record of clinical and commercial success. Many of these drugs are known as 'me-too' or follow-on products, because they constitute similar or slightly modified formulations of existing approved therapies. In the UK during the 1970s over 80% of new drugs fell into this class (Goodman, 2000). Often the aim of a new 'me-too 'drug is to offer a marginal improvement in either the safety or efficacy of an existing product.

Since the 1980s pharmaceutical companies, needing to maintain their historic levels of revenue and profitability, have grown increasingly reliant on a number of 'blockbuster drugs'

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[1]   The term 'target' refers to the molecular site within the cell at which a drug may act. Normally such sites are molecules that are involved in 'disease pathways' – the sequence of interacting molecular and cellular events that ultimately cause pathology. The concept of a target is similar to the idea of a drug receptor, which according to Boston University is "...small, chemically defined areas (of a cell) which give (initiate) a biological response upon uniting with chemically complementary areas of natural or foreign molecules (drugs)". (Boston University Medical College [online], 2006).

(Kadens and Le Gear, 2000), which are defined as products with over \$1 billion in annual sales. This in turn has allowed the industry to sustain its extremely high R&D spending and the broad product pipelines of many companies. Broad drug development pipelines are another method of spreading risk by having a range of products in ongoing development at any one time. This is an expensive process. However, many blockbuster drugs are follow-on products, usually aimed at common chronic diseases, which require the long-term treatment of patients (Kraft, 2004). These markets are valuable, but are becoming increasingly crowded with competing products. Furthermore, patents on a significant number of blockbusters are close to expiry and there may be a limit to the number of 'follow-on' products that can be derived from any one formula. The industry's increasing reliance on blockbuster products to fund the growing expense of research has highlighted not only the crisis in productivity, but also the potential dangers of being over reliant on a commercial strategy that may not be indefinitely sustainable. This has prompted the search for new sources of innovative products and increasing investment in molecular biology, biotechnology and genomics.

3.2 The impact of genomics on drug discovery and development

If the 1980s were the era of blockbuster pharmaceuticals, the 1990s saw the rise of biotechnology based on recombinant DNA technology. The first successes of biotech were biopharmaceuticals (See Chapter 4) largely developed in the previous decade, with several therapeutic proteins, such as recombinant insulin and EPO, becoming blockbusters in their own right. However, the initial applications of recombinant DNA lay in creating new biological manufacturing processes and had little immediate bearing on the discovery and development of the small molecule drugs that were the main product focus of large pharmaceutical companies. Only following the advent of the Human Genome Project (HGP) and the coming of genomics in the mid-1990s did new technologies based on biology start to have a significant impact on the process of creating new medicines within the mainstream pharmaceutical industry.

There is no agreed definition of genomics. According to the Human Genome Program of the U.S. Department of Energy Office of Science (2003), genomics is 'the study of genes and their function'. However, many researchers would stress that genomics is concerned with the study of all genes in an organism (the genome) and is often done on a large scale. In particular, genomics involves the use of a range of techniques, such as high-speed sequencing and the analysis of genetic variants (polymorphisms) and gene expression, and offers the possibility of understanding the relationship between genes, proteins and disease.

The discovery of new genomic drug targets

The main attraction of genomics to the pharmaceutical industry has been the promise of discovering thousands of new and potentially novel targets for the development of small molecule drugs from the pool of 20-30,000 human genes. These targets would be the genes and proteins involved in causing disease, and could ultimately provide a new generation of blockbuster drugs. This prospect has stimulated billions of dollars of pharmaceutical industry investment in genomics, both through the development of in-house activities and over 2,000 collaborations with smaller genomics and biotechnology firms.

Several hundred dedicated genomics companies have been founded in North America and Europe, often with the intention of supplying new drug targets and early stage small molecule products to large firms. This strategy was based on the assumption that new drugs based on novel genomic targets would be better candidates for entering clinical trials, thus providing a boost to both innovation and productivity. However, this has proved more difficult than first

expected and whilst the initial identification of genes involved in disease has been relatively simple, validating the exact role these genes play in disease and developing new drugs based on this knowledge has been difficult. To make best use of genomics-derived information requires an understanding of the interactions of genes and proteins with each other and their environment at molecular, cellular and system levels. This complex biological information has not been as forthcoming as simple target identification and will take a great deal of time and effort to evaluate and understand.

Pharmacogenomics and pharmacogenetics

In the last five years the focus of post-genomics research has focused increasingly on the function and expression of genes, and on studying the variations within and between different human populations. This has sparked growing interest in the two closely related areas of pharmacogenomics and pharmacogenetics. These two terms are often used interchangeably, but for the purposes of this report will be defined more carefully.

Pharmacogenetics is best understood as the study of the genetic basis of drug response and is mainly concerned with the assessment of a drug's clinical efficacy and/or safety profile. It is primarily focused on understanding how an individual's response to medication may be affected by their genetic make up (genotype).

In contrast, **pharmacogenomics** is best described as being concerned with providing a comprehensive, genome wide assessment of the effects of pharmacological agents on gene expression patterns (Lindpaintner, 2004). This information is used to evaluate the different effects of a number of chemical compounds during the process of choosing the best one to develop (so called 'lead selection') and does not focus on differences between individuals.

Pharmacogenetics therefore proves useful in clinical studies to find the medicine best suited to a given patient (or to find the patients most likely to respond positively to a drug). In contrast, pharmacogenomic studies are used during the process of drug discovery and lead selection to find the most suitable drug candidate from a given series of compounds under evaluation.

3.3   Pharmacogenomics and drug discovery

The use of genomic information in drug discovery

Apart from the identification and validation of new drug targets, one of the main applications of genomics within the pharmaceutical industry has been to help select the best drugs to develop for a particular target (lead selection). Normally this process involves assessing the most optimal configuration of a small molecule drug, which has been identified as a lead candidate for clinical testing. Medicinal chemistry is often used to create a number of closely related variants of the compound and these are then screened in a series of animal models to assess their performance *in vivo* with regards to efficacy and safety. This type of screening is expensive and can now be augmented and partially replaced by looking at the effect a drug has on a set of marker genes in cell culture (so called 'expression profiling') (Lindpaintner, 2002). This involves using microarrays (see Chapter 2) to scan the response of particular groups of genes to the presence of different drugs. Microarrays are massively parallel screening devices and can assess the response of a large number of genes (or proteins) at the same time. This 'pharmacogenomic snapshot' gives a genetic (or protein) response profile of the drug being tested. Expression profiling can be used to either identify any potentially toxic reactions the drug may cause (known as toxicogenomics) or to assess the specificity of the

drug against its intended target (i.e. the extent to which it binds only to that target). It is hoped that the early use of pharmacogenomics in the drug discovery process will help select compounds which are more likely to achieve market success, thus reducing the attrition rate and improving productivity.

Pharmacogenomic disease stratification and the development of new cancer therapies

Another important application of pharmacogenomic gene expression profiling has been its use in helping understand the precise molecular mechanisms involved in causing particular diseases. For example, during the development of cancer, a number of complex genetic changes occur to the cells in the tumour. These include mutations in the DNA caused by environmental factors (such as pollution and smoking), as well as more complex chromosomal rearrangements. They are referred to as 'somatic mutations' and are distinguished from inherited genetic defects, as they cannot be passed on to the next generation. Such genetic changes lead to altered patterns of gene expression, which can be detected by pharmacogenomic studies and this information has been successfully used to develop a new group of targeted (or so called 'designer') cancer therapies. A good example of these therapies is Imatinib (Glivec in the UK and Gleevec in the US), which is designed to target specifically the molecular mechanisms involved in causing cancers. Whilst Glivec has enjoyed some measure of success, other targeted cancer therapies have proved less viable. In 2003 Iressa (AstraZeneca) was initially fast tracked for approval as a drug of final resort for lung cancer patients for whom all other therapies had failed (Langreth, 2004). However, in December 2004 the FDA announced that, following a postmarketing clinical trial, Iressa had failed to show any survival advantage compared to a placebo (FDA, 2004b). The FDA is currently evaluating the results to determine if Iressa should be withdrawn from the market. Despite this, erlotinib (Tarceva) (OSI Pharmaceuticals and Genentech) another anti-lung cancer drug with a similar mode of action to Iressa, was approved by the FDA in November 2004 (FDA, 2004c). OSI/Genentech's Tarceva blocks growth factor proteins from binding to tumour cell receptors. It is hoped that by doing this, it may be possible to prevent further growth of the tumour cells.

Case study: Imatinib (Glivec) – a genomically targeted therapy

Imatinib mesylate, sold as Gleevac in the United States and as Glivec elsewhere is produced by Novartis. It is available in oral capsule form as a treatment for Chronic Myeloid Leukaemia (CML).

CML accounts for some 15-20% of leukaemia cases (Drucker, 2002). Almost all CML patients have a chromosomal abnormality known as the 'Philadelphia chromosome', which produces a mutant and overactive protein (Charatan, 2001). This abnormal protein is responsible for triggering the excessive cell proliferation characteristic of cancer. It is as a result of this genetic abnormality that the resulting overactive protein causes excessive cell proliferation and destabilisation. With CML the affected cells are clonal haematopoietic stem cells and the white blood cells they produce. Glivec acts by blocking and inhibiting the activity of the mutant protein (known as bcr-abl) thus negating its effects. It acts as a highly specific enzyme inhibitor.

Glivec has had considerable clinical success in treating CML, with the vast majority of patients who are treated in the initial chronic phase of the disease achieving a complete remission. This compares to lower remission rates and high side-effects following alpha interferon treatment, and poor long-term prospects with chemotherapy alone (Drucker, 2002). Aside from Glivec, the only cure for CML is a bone marrow transplant, which relies on a suitable donor being found and on the patient being in a robust enough condition to survive the surgery. Due to the fact that a known chromosomal abnormality is directly involved in causing the disease, CML can be diagnosed, even before symptoms appear, through routine blood testing and a DNA test, which can reveal the presence of the Ph chromosome. This allows more patients to be identified while still in the early stages of the condition. Early detection is important because late stage leukaemias often develop resistance to Glivec and other drugs, and prove incurable.

Glivec has also received attention because of the mechanism of its action. As well as being a rationally designed drug, it may also target a disease pathway common to other cancers during their development. It was initially designed to target a different mutant protein of a similar type to bcr-abl – a tyrosine kinase – which was thought to be involved in the development of gastrointestinal tumours (Drucker, 2002). Other tumours, including types of breast, lung, prostate and skin cancer, may use similar pathways, although it is unlikely that a mutant tyrosine kinase is the sole agent responsible for the malignancy in many of these tumours. Even if Glivec does not prove as successful in treating these other forms of the disease, it can be seen as an endorsement of the model of targeting the molecular basis of pathogenesis in cancer and identifying those molecular features which can help target specific therapies at the patients they will help most.

In May 2001 Glivec was approved for use in the US in CML therapy for all stages of the disease, once interferon alpha treatment has failed. By November 2001 the US had been followed by Switzerland, Australia and Europe (Habeck, 2002). Glivec was one of the first molecularly targeted anti-cancer drugs. In 2003 Novartis recorded worldwide sales of Gleevac/Glivec of $2.2 billion, making it the company's second best-selling pharmaceutical product (Novartis, 2003).

3.4   Pharmacogenetics

3.4.1   What is pharmacogenetics?

It has been known for many decades that individuals differ in the way they respond to a given pharmaceutical therapy and one reason for this lies in the genetic variation between individuals (Schmedders *et al*, 2003). Following the sequencing of the human genome, the aim of much 'post-genomic' research is to translate DNA sequence information into useful medical knowledge, including novel therapeutic and diagnostic products. The promise of pharmacogenetics is to apply new data about genetic variation to understand the problem of differential responses to medication (Lindpaintner, 2002). Although most drugs are designed and regulated to work in the entire population, it is widely recognised that there are significant variations between individuals in both the safety and efficacy of medicine. Variations in drug efficacy mean that medicines do not provide the intended benefit for every patient, with a significant number of people simply not responding to treatment. Differences with respect to drug safety can result in serious adverse drug reactions (ADRs), which cause major health problems or even result in death. It has been estimated that ADRs are the fourth biggest cause of death in the USA (May, 2004). A significant proportion of ADRs and lack of efficacy may be attributed to genetic factors, although the influence of behavioural and environmental factors should not be underestimated (Audit Commission, 2001). One of the potential advantages of pharmacogenetics lies in matching the natural variation in a person's genetic make-up (their genotype) to their response to specific pharmaceutical products. This might enable the prescription of medication to be tailored to an individual's genotype, allowing the development of so-called personalised medicine. In principle, this could both reduce safety problems and improve the effectiveness of treatment.

The introduction of personalised medicine rests on two key ideas: 1) The stratification of patient populations according to their response to a particular medication. This may include the identification of groups of patients who are at risk of ADRs (safety) or those patients who respond well to therapy (efficacy). 2) The stratification of diseases into specific subtypes that are categorised according to genomic criteria and by their response to particular treatments in a fashion similar to that outlined in Section 3.3 above (Shah, 2003). This has also been occurring in relation to a number of common diseases, such as certain cancers, which have been stratified into distinct disease sub-types, as well as a number of viral diseases (HIV and hepatitis infection – see below). The potential benefits of disease stratification would be to improve diagnosis and in some cases link this more closely to therapeutic options.

A key factor in the potential development of pharmacogenetics is that disease and patient stratification would also involve the segmentation of drug markets. This fundamentally threatens the cornerstone of pharmaceutical industry profits - the blockbuster drugs that are sold universally into an undifferentiated market. Fresh knowledge about human genetics has been heralded by some as a potential saviour for the industry, with claims that it could both greatly reduce the costs of drug development and supply thousands of new drug targets. To gain these benefits, however, pharmaceutical companies might have to make major changes: namely, a drastic restructuring of operations to account for genetic variability. Implementing such changes will not be easy, and the pharmaceutical industry is faced with difficult decisions about the extent of its commitment to change in this area.

3.4.2 Different approaches to pharmacogenetics and their potential benefits

A number of discrete options for the clinical and commercial application of pharmacogenetics can be identified. The most realistic of these are described briefly below:

Pharmacogenetics to improve drug discovery

Pharmaceutical companies are increasingly using pharmacogenetics (PGx) techniques and data to improve the drug discovery process. There are two main ways in which this is being done.

1) *Discovering new drugs that work well in the entire population*
Drug candidates can be screened for variable response against the most common variants (alleles) of a particular genomic target (i.e. gene that is involved in disease). Only those candidates who show no significant variation in efficacy are then taken into drug development. This type of screening reduces the risk of drugs being rejected at a later stage and increases their likelihood of success. Drugs developed this way are more likely to work well in all patient groups.

2) *Discovering new 'pharmacogenomic' drugs aimed at genomic sub-populations*
A number of companies are developing strategies to create new drugs aimed at particular genomic sub-populations; this is what has been called 'pharmacogenomics' (see above). In most cases the target groups will be individuals who are most likely to benefit from therapy, so called 'good responders'. These drugs would probably have to be approved as safe in all groups, but would be licensed and marketed for good responders. In principle, this might increase the chance of an effective drug being approved, but at the expense of it having a restricted market. If such drugs were developed they would be more likely to be clinically effective in their target group, but might also be considerably more expensive.

Pharmacogenetics to improve the safety and efficacy of drug development

One of the main ways PGx may have an impact on drug development is in the design and analysis of clinical trials, with a number of authors claiming that this will lead to smaller, smarter and cheaper trials). (Rothstein and Epps, 2001; Roses, 2000b). Others have suggested that drugs causing ADRs in particular genomic groups could be 'rescued' in late stage trials. A third possibility would be to target drug development at patients most likely to respond to a therapy.

1) *Pre-clinical testing and the redesign of early clinical trials*
In early, pre-clinical studies or in early stage Phase 1 clinical trials, genotyping might be used to either exclude or include particular genomically defined groups in order to increase the chances of a drug being shown to be safe (Issa, 2002). However, this type of pre-screening is likely to meet significant opposition from regulatory authorities, due to the risk of missing serious ADRs. It seems more likely that companies will actually use PGx to ensure that trial populations are representative of the general population for particular genetic variants associated with drug metabolism (e.g. CYP2D6). This could greatly help to minimise the risk of trial bias, or reduce the risk of a drug failing at a later stage of development as a result of bias, and to improve the safety profile of the final product.

2)   ***'Rescue' of products in late stage trials due to ADRs***
In later stage Phase II and III trials, PGx may be used retrospectively to identify particular genomically defined groups who are at higher risk of ADRs. This might be particularly important in 'rescuing' a therapy that was highly effective, but was associated with a small number of serious genetically based ADRs. These groups could be identified and excluded from subsequent pivotal trials. A drug developed in this way would only be licensed for use in specific sub-populations and would need careful monitoring, because of the risk of it being given to the wrong patient group. Consequently, it would have to be used in conjunction with a test for pre-prescription genotyping and have a restricted market. Regulators might license such a product solely for use in specialist secondary and tertiary settings, due to the higher risk of off-label prescribing in primary care.

3)   ***The creation of new drugs for particular sub-populations of 'good responders'***
In later stage Phase II and III trials PGx might be used in two ways to improve efficacy. First, prospective studies could test new drugs in sub-populations of patients believed to be good responders. This might significantly increase the chance of a drug reaching the market. Second, where the overall benefit of a drug across the whole population is shown to be marginal, PGx might be used retrospectively to identify a particular genomic sub-group who are particularly good responders to the therapy. These groups could be specifically included in subsequent pivotal trials. In both cases this would lead to the development of new drugs licensed for use purely in a specific genomic group. The breast cancer therapy Herceptin (trastuzumab) is an example of a very successful product developed for a genetically defined group of patients whose tumours over express the HER-2 gene product. Whilst this drug is largely safe in all patients, it is only effective in this sub-population.

Improving the prescription of licensed drugs

Much attention has been given to the ways in which PGx might benefit the pharmaceutical industry in the discovery and development of new drugs. However, the technology offers significant advantages to clinicians, healthcare providers, patients and companies by improving the purchase, prescription, use, marketing and surveillance of licensed products. This might be achieved in a number of ways.

1)   ***Extending the use of products restricted by ADRs***
A number of approved drugs already have restricted markets as a result of safety problems. For example, the HIV/ AIDS drug Abacavir (see case study) requires very close monitoring for the first few months of its use due to a severe hypersensitivity reaction in ~5% of patients. This places limits on its clinical use. Trials are currently underway to identify the genomic sub-group most at risk of this ADR, so that pre-screening can be used to exclude them from therapy. Such strategies might be used to extend the uses of drugs with practice and label restrictions, and result both in therapy for a greater number of patients and in increased product sales.

2)   ***Pre-prescription screening to identify patients at risk of ADRs***
One of the most widely publicised applications of PGx is the development of 'personalised medicine' in which patients are genotyped before medication to enable physicians to give 'the right drug to the right person'. Attention has focused particularly on the possibility of pre-prescription testing to identify patients at greatest risk of genetically based ADRs resulting from the use of a given drug. These patients could either be offered an alternative therapy or be closely monitored, if no alternative

exists. A number of laboratories and private companies in the USA already offer thiopurine methyltransferase (TPMT) genotyping to identify patients most at risk of severe adverse reactions as a result of their inability to metabolise the chemotherapy drug 6-Mercaptopurine (see case study). This type of application of PGx is attractive to doctors, patients and healthcare providers, as it would lead to safer prescription and reduce the burden posed by serious ADRs.

3) *Post-marketing surveillance of approved drugs*
    Pharmacogenetics could also be incorporated into improved post-marketing surveillance of medicines. Patients who have suffered an ADR could be genotyped to see if there was a genetic basis for their response. This might lead to the creation of a test to identify people at high risk of rare ADRs. Rather than leading to drug withdrawal, the introduction of this form of PGx testing might also enable some products to remain on the market (Robertson, Brody, Buchannan, Kahn, & McPherson, 2002 p.158) or to be 'rescued' after withdrawal (Issa, 2002). However, regulators have indicated that this latter option is unlikely to win much support.

4) *Pre-prescription screening to identify 'good responders'*
    In a similar fashion to pre-prescription patient safety testing, PGx could be used to identify those most likely to respond positively to a specific drug. It is already well established that some patients fail to respond to common prescription medicines such as Prozac. There have been claims that testing for non-responders would be cost-effective for health-care providers, as the expense of genotyping would be more than offset by savings from reducing ineffective prescription (Lichter & Kurth, 1997). In some cases this might lead to an overall reduction in healthcare costs (Robertson, Brody, Buchannan, Kahn, & McPherson, 2002). However, the use of PGx by purchasers to reduce the overuse of ineffective drugs in groups of non-responders clearly conflicts with the interests of the pharmaceutical industry as it is predicated on reduced drug sales (Robertson, Brody, Buchannan, Kahn, & McPherson, 2002).

5) *Use of efficacy data in drug marketing*
    Pharmacogenetic information could allow doctors to make a more informed choice about the use of one medicine compared to another in the same drug class. This might also provide some pharmaceutical companies with a powerful marketing tool if they could demonstrate that their medicine was more effective in a particular patient group than a rival product. Such a prospect would be particularly attractive to companies whose products were lower ranked by sales volume.

3.4.3 Products currently in use or under development

Products currently in use

A small number of pharmacogenetics products are already on the market (see Table 3.2), the most common of which are tests to detect variants in drug metabolising enzymes for use in pre-prescription genotyping to prevent ADRs. One of the best-known examples of genes that affect the rate of drug metabolism is the Cytochrome P450 (CYP) gene family. The CYP2D6 gene is believed to be involved in metabolising 25% of all currently prescribed medicines including beta-blockers (for heart disease) and anti-depressant/anti-psychotics (Nuffield Council on Bioethics, 2003). The reason drug metabolism is important is because slower than normal metabolism can cause a drug to remain in the body for longer than it otherwise would and concentrations may build up to harmful levels. Alternatively, a very fast metaboliser would eliminate the same drug from their system before it could have a full therapeutic effect

and so they would not gain much benefit from the treatment. Knowledge of a patient's CYP status could therefore be a useful prescribing aid and might help doctors to choose the right dose of a medication to give to particular individuals. Roche Diagnostic's AmpliChip CYP450 is a DNA microarray, which analyses variations in two genes in the CYP family-CYP2D6 and CYP2C19, the latter gene's products being involved in metabolising anti-epileptic drugs among others. The AmpliChip detects two major variants of CYP2C19, producing predictive categories of poor and extensive (normal) metabolic activity, and distinguishes 29 polymorphisms in CYP2D6 indicating the patient as a poor, intermediate, extensive or ultra-rapid metaboliser.

Other current tests, such as such as the Oncotype test (see table 3.2) or testing for HER-2 status for use with the drug Herceptin (see monoclonal antibodies section for case study), are attached to a particular marketed product. These tests are often used to stratify patients to identify particular response groups. In the case of the HER-2 test, a biochemical test is used to identify a genetic subset of breast cancer patients whose tumours are susceptible to Herceptin treatment. The Oncotype test works slightly differently by genetically stratifying breast cancer patients on the drug tamoxifen, according to their likelihood of a future relapse of the disease. Both tests share the aim of focusing treatment where it is most effective and avoiding unproductive drug use. A third type of available pharmacogenetic test is the analysis of infectious agents, such as Hepatitis C Virus and HIV-1. Although these tests do not measure any human genetic characteristic, they are used to detect viral strains that are resistant to a particular drug and have the effect of stratifying patient groups according to therapeutic response. Hepatitis C genotyping can determine the duration of treatment while other tests such as Digene's Hybrid Capture II (see Table 2.1) test can separate human papillomavirus infections into low and high risk categories for the potential to cause cervical cancer. However, metabolic profiling tests are limited in their utility as drug response and toxicity are often the result of complex interactions between genes, the environment and behaviour, including poor compliance with treatment regimes (Tucker, 2004). Other product-specific tests are limited in effectiveness to small sub-sets of patient groups and may be restricted in use by economic factors (see Section 3.4.3 below).

Products under development

A range of other pharmacogenetic tests are in development, examples of which are shown in Table 3.3. These new tests are aimed either at providing improved choices for the use of existing, approved drugs such as statins, chemotherapy drugs and treatments for rheumatoid arthritis or are intended to be developed in concert with new drug products. Along with many of the tests for existing drugs, diagnostics are being designed to stratify patients into good responder groups for particular therapies. Similarly, other tests such as Ovanone, Hypertension Rx and Neurological Rx are also intended to select the most potentially beneficial therapies from a range of existing drugs depending on genetic response profiles.

Some of these tests are being designed to work with a specific drug – Clozapine, Abacavir (see case study) or with particular classes of drug, such as the statins. These tests are designed to detect genetic subgroups within the patient population for the relevant condition. Abacavir is an anti-HIV drug, which has a serious, potentially fatal hypersensitivity side effect in a small minority of patients. Clozapine, a schizophrenia treatment also affects a sub-group of patients with a potentially life threatening ADR involving white blood cells. In both cases a test is being sought to identify genetically individuals at greatest risk. All of these tests being developed for existing drugs are intended as pre-prescription tests to aid clinical decision-making.

Table 3.2 Examples of established commercial pharmacogenetic tests

Test	Factor Measured	Company	Applications
CYP2D6/ CYP2C9/ CYP2C19/ CYP1A2	Metabolism rates of many common drugs	Genelex	Genelex offer laboratory screening for variation in the genes CYP2D6, CYP2C9, CYP2C19, and CYP1A2. Knowledge of variants in these genes can help physicians predict individual responses to many prescription, OTC (over-the-counter) and herbal medicines, including warfarin, prozac, zoloft, paxil, tamoxifen, and valium. The aim is to prevent adverse drug reactions by classifying patients as having poor, intermediate, extensive and ultra-extensive rates of metabolism for a variety of common drugs.
PRO-PredictRx TMPT Genetics	Rheumatic Disease	Prometheus Laboratories	PRO-PredictRx TMPT Genetics measures the level of TMPT enzyme activity in patients with rheumatic disease to determine patient candidacy and dosage for IMURAN therapy.
Onco*type* DX	Likelihood of breast cancer recurrence in women treated with tamoxifen	Genomics Health	Onco*type* DX is a diagnostic assay that quantifies the likelihood of breast cancer recurrence in women with newly diagnosed, stage 1 or 2, breast cancer who will be treated with tamoxifen. The test involves assessment of a patient's tumour tissue sample for variation in a panel of 21 genes associated with recurrence or non-recurrence in particular sub-types of breast cancer. The aim of the test is to provide enhanced treatment planning by stratifying patients according to likelihood of recurrent disease.
ViroSeq	Viral genotyping	Celera Diagnostics	HIV-1 genotyping in human blood samples to detect drug resistant strains and mutations. Allows patient stratification for appropriate treatment regimen selection.
Hepatitis C Virus (HCV) genotyping kit	Viral genotyping	Third Wave Molecular Diagnostics	A set of reagents for Third Wave's Invader laboratory nucleic acid testing technology allows HCV infected samples to be identified as carrying one or more of the six major subtypes of the virus by genotype. This allows informed decision making about treatment, as different viral subtypes have different drug resistance profiles.

Case study: Thiopurine Methyltransferase (TPMT) – benefits and limitations of pre-prescription pharmacogenetic testing

Thiopurines are a class of drug developed during the 1950s, which are used primarily to treat leukaemia (Purinethol, Lanvis) and suppress the immune system to avoid organ rejection during transplants (Imuran) (European Commission, 2004). Despite general success, a small number of patients have been found to suffer dangerous, even fatal toxicity as a result of thiopurine drug treatment. The enzyme Thiopurine MethylTransferase (TPMT) is responsible for metabolising the thiopurine drugs in the body (van Aken, 2003).

To date several variant forms (alleles) of the TPMT gene have been discovered, which are associated with a reduced ability, in varying degrees, to metabolise thiopurine drugs (Ibid.). TPMT activity can be measured phenotypically through taking a red blood cell count, or genotypically using genetic testing methods developed in the 1990's. It is known that reduced TPMT activity can cause toxic ADR's. Currently the red blood cell count (RBC) is recommended on the European labelling of thiopurine drugs (European Commission, 2004), but genetic testing is also used to assess patient risk. Testing kits are available and a number of diagnostic labs in Europe and North America offer their own in-house testing service for patient samples. Although TPMT testing has been around for some time, its uptake has been affected by a number of factors. In particular, it is slower than the RBC count method and has a significantly higher cost. There are also issues over its applicability across populations, as a marker for increasing dosage, and in its detection rate of ADR's (Shah, 2004).

Much of the research on TMPT mutations to date has been carried out on populations of European descent, and has detected four common alleles associated with TPMT deficiency (Ibid.). However, the smaller number of tests in other populations, mainly Asian, have shown that different alleles are most likely to be important in different populations and some groups, such as populations from Latin America, have had no data gathered yet (van Aken, 2003). In order for truly widespread use of pharmacogenetics reliable data on all populations needs to be collected.

A clear correlation between impaired TPMT activity and serious side effects has been established, but this only accounts for a fraction of the total number of ADR's experienced by thiopurine-using patients. On average 78% of thiopurine adverse effects are not due to TPMT variants, but to other factors such as possible interaction with other drugs and variation in other ADME enzymes (Ibid.). TPMT testing can still provide valuable information for patient stratification, but it cannot remove the need for close monitoring of patients on drugs with known side effects.

As well as avoiding ADRs, pharmacogenetics offers the possibility of treating identified rapid-metabolisers of a drug with increased dosages. However, the by-products of thiopurine metabolism can themselves have potentially dangerous effects on the liver. An increased dosage would lead to greater levels of these by-products, so increasing the risk of an adverse reaction, as well as potentially exacerbating the ADR's that are not due to TPMT status. TPMT testing has the potential to provide useful, potentially lifesaving information to doctors before treating patients, but it cannot reduce the need for patient oversight or for the need to fully investigate the effects of increased drug dosages on the body. Ultimately TPMT tests the effects of a single gene, which is only one part of a complex system. It should be noted that no DNA based TPMT test is currently in routine use in the NHS.

Tests being developed in conjunction with new drugs are being used in a different way, as these tests are intended to assist the development of the new products. Clinical Data's Vilazodone is an anti-depressant of a similar type to Prozac, currently in Phase I/II clinical trials. At this stage it appears to have a suitable safety profile and shows signs of efficacy. However, many drugs in clinical development prove safe, but fail large-scale Phase III clinical trials because they simply do not show a significant level of health improvement in patients. With Vilazodone, Clinical Data are profiling patients before the later stages of clinical testing to identify genetic subgroups who may have a good response profile to the drug. Unlike other examples given in Table 3.3, this search for good responders is occurring before attempting the approval process. NeoPharm are also using pharmacogenetic profiling in the development of their anti-cancer drug LE-SN38. In this instance the profiling is used to find groups with different rates of metabolism of the drug, based on variations in a liver enzyme known to break down LE-SN38. In this way, dosage levels can be set to avoid ADR's during the early safety testing stages of clinical development. Both these tests could help companies to get approval for their respective drugs by structuring clinical trials in such a way as to target good responders or avoid poor ones (Lichter & Kurth, 1997).

3.4.4   Clinical Use and Practice Issues in pharmacogenetics

In order to successfully introduce pharmacogenetics products into health services and routine clinical work, a number of organisational and practice issues will need to be considered. These include the types of disease that will best suit a PGx approach, the availability and efficacy of existing therapies, and the cost effectiveness of employing a pharmacogenetic approach in a given situation.

Medical Need

The seriousness of the disease and the severity of possible side effects play an important role in determining where PGx approaches are likely to be successful. For mild conditions or those that are easily or rapidly treated there is little incentive at present to develop or to use relatively expensive genetic testing. Similarly, if the potential side effects of a drug are mild then the cost of alleviating them is likely to be less than the cost of ordering a PGx test. However, in severe and chronic diseases or when side-effects are potentially dangerous and it is important to avoid ineffective or harmful courses of medication, then the potential utility of a PGx test is significantly increased. Cost saving through the avoidance of ineffective therapy is also important to healthcare providers where expensive medicines are involved. The case of Abacavir provides a good example of an expensive treatment for a serious condition (HIV infection) and where adverse reactions can have costly and medically severe outcomes (see case study). Another major area of application for pharmacogenetics is in oncology where the therapeutic window is narrow (i.e. the difference between giving an effective dose and a toxic dose of a chemotherapy is small). As a consequence, a number of PGx tests are being developed to aid the dosing and choice of cancer therapy.

There are also issues around the practicality of introducing pharmacogenetic methods into routine prescribing. For example, patients who are receiving anti-psychotic medication, such as Clozapine, may benefit from PGx testing. However, they may be unwilling or unable to sustain a regular and prolonged course of treatment, thus ruling out this therapeutic option (Webster *et al*, 2004). In such cases, pharmacogenetic testing could also add further complexity to an already involved prescribing process.

Table 3.3 Commercial pharmacogenetics tests currently in development

Test	Disease	Company	Application	Stage of development
Ovanome	Ovarian Cancer	DNAPrint Genomics	Genomic-based diagnostic tool to match ovarian cancer patients with the most suitable form and dose of chemotherapy. Detects SNP alleles that are predictive for non-response to the Taxol and Carboplatin drug chemotherapy combination.	Laboratory validation.
Statinome	Various cardiac disease, high cholesterol		PGx test to classify patients as adverse responders or good responders to the statin class of drugs. Statins are used to treat patients who are at increased risk of heart disease.	Laboratory validation.
Vilazodone & test	Depression	Clinical Data	Vilazodone is a small molecule compound Clinical Data have licensed from Merck, for the treatment of depression.	Entered phase II clinical trials in 2005 and start of test development.
Statin Tests	Hypercholes-terolaemia		Clinical Data carried out a clinical study to find correlations between genetic variation and response to statin treatment for high cholesterol. They are now attempting to develop a predictive response test from this data.	Pre-clinical development.
Clozapine Tests	Schizophrenia		Results from a Clinical Data study on genetic variation and response to the schizophrenia drug Clozapine is aimed at identifying a subset of patients who are most likely to develop agranulocytosis, a potentially life-threatening depletion of white blood cells.	Initial study still in progress.
Hypertension R$_x$	Hypertension	Prediction Sciences	Pre-prescription testing to predict which anti-hypertensive medication therapy (ACE, Ca-Channel or ARB Inhibitor, diuretic, ß-Blocker, combination) would be most effective for lowering the patient's blood pressure upon diagnosis.	Pre-clinical development.

Neurological R$_x$	Depression, bipolar disorder and schizophrenia		Pre-prescription testing to predict response of a patient for treatments in depression, bipolar disorder and schizophrenia. Most anti-psychotics or depression medications have a non-response rate of 50% or higher, and schizophrenia is one of the most expensive diseases to treat.	Pre-clinical development.
LE-SN38 Genotyping	Early stage clinical development	NeoPharm	NeoPharm have employed the genotyping of patients in the early pre-clinical and clinical development of their anticancer drug LE-SN38. Genotyping splits responders into regular and slow metabolisers and allowed for dose safety adjustments.	LE-SN38 completed phase 1/2 clinical trials.
CYP2D6 and CYP2C19. Genotyping kits	Drug metabolism	Gentris	Development of kits for pre-prescription diagnosis for providing point-of-care genetic testing to physicians. CYP gene variants affect the metabolism of various drugs	CYP2D6 kits available as "investigational use only" Seeking FDA approval in 2006.

Case study: Abacavir (a pharmacogenetics test in development)

Abacavir is an anti-HIV-1 drug manufactured by GlaxoSmithKline and marketed as Ziagen. It received approval from the FDA in 1998 and in Europe in 2000. Abacavir belongs to a class of drug known as a nucleoside reverse transcriptase inhibitor (NRSI). The HIV-1 virus uses an enzyme, reverse transcriptase, to replicate when it invades a host body cell. Abacavir binds to the active site of the viral reverse transcriptase enzyme and inhibits production of a function viral DNA molecule. This effectively stops the HIV virus from replicating and it can no longer act to damage the host cell. Worldwide sales of Ziagen were $274 Million in 2003 (Baysden, 2004). A small subsection of around 5-9% of HIV-1 patients show a hypersensitivity reaction to treatment with Abacavir, which can potentially be fatal in a small number of cases. There are good reasons for assuming there is a genetic component to this susceptibility, which could be identified by pharmacogenetic methods, and a high medical need to identify patients at risk of fatal toxicity.

A number of association studies have been carried out including those by investigators at GSK and by a group in Australia to investigate links between prospective gene candidates and the incidence of hypersensitivity reactions amongst Abacavir patients. The major contenders for cause of this ADR are different alleles (versions) of genes in the Human Leukocyte Antigen (HLA) family. In addition, the gene HLA-B57 has been identified as being a useful marker for Abacavir hypersensitivity susceptibility. However, its sensitivity as a marker ranged between 55% and 78% accuracy. The clinical utility of a test depends on avoiding both false positive results (where people would be wrongly identified as being hypersensitive to Abacavir and perhaps denied access to the drug) and false negatives (where individuals would be assessed as safe and still be at risk of suffering an ADR). Some diagnostic labs do offer a genotyping service based on the HLA-B57 gene, but this is not endorsed by GlaxoSmithKline due to its uncertain predictive validity. Further studies have identified two or three sets of marker genes, which may provide sufficient predictive powers to be used as the basis for a clinical test for hypersensitivity.

It is hoped that an accurate test can be developed to use in conjunction with the drug, so that the drug label can be rewritten enabling it to be given to a greater number of patients without risk of serious side effects.

Reliability of genetic testing

Pharmacogenetics is inextricably linked to the process of genetic testing. To be of clinical utility, tests must be accurate in predicting a patient's status. They should not produce an unacceptable level of false positive or false negative results. They should also provide accurate information when applied within and across different populations. This has been a significant limitation of the TPMT test (see case study above). Finding a relevant gene and developing a test for it is a complex and time consuming process. In many cases of ADR's and rare response types, the number of patients involved is very small and this makes it very difficult to establish a reliable basis for associations between genetic markers and drug response. For other conditions, such as lung cancer, tissue samples are not routinely taken on account of practical difficulties (Herper, 2002), so trying to establish a genetic basis for response to a targeted cancer therapy in non small-cell lung cancer will require a considerable research effort. Genetic tests for PGx face all the same difficulties in validation and establishing accuracy as genetic testing for other purposes (see Chapter 2). Ultimately, successful tests should be easy to perform, reliable, relatively inexpensive and easily interpretable, if they are to be incorporated into clinical practice. The biochemical test for

HER-2 over-expression and Herceptin prescription uses well-established methods and readily available equipment and so was rapidly adopted for clinical use once it gained regulatory approval.

Cost effectiveness

In order to become widely integrated into clinical practice pharmacogenetic tests must not only be reliable and valid but must also prove cost effective (see review by Philips and Van Bebber, 2004). The criteria for doing this are similar to other medical interventions, with an emphasis on the added value of the test. Pharmaceutical companies are under pressure to maintain profits when producing and deploying pharmacogenetic tests and associated drugs, while both public and private healthcare systems must aim to constrain costs in order to remain viable. For drug companies, PGx testing offers the possibility of targeting new drugs in development to specific genetic populations where they will be most efficacious and of adjusting dosing levels appropriately to avoid ADR's. This use of pharmacogenetics would help get more drugs approved and possibly allow smaller clinical trial cohorts, both of which would save money in the development process (Lichter & Kurth, 1997). However, patient stratification could also reduce the potential market size for new (and existing) drugs, if they are targeted only at certain genetically suitable sections of the overall market (Shah, 2003). Similar concerns also affect pharmacogenetic tests which stratify the market for existing drugs, although dose stratification or avoidance of severe ADR's in small sub-sections of the overall patient population are seen as less controversial applications of PGx (Ibid. Shah, 2004).

Healthcare organisations could also potentially make cost effective use of pharmacogenetic testing. This is most likely to occur in treating patients with chronic illness, where expensive long-term pharmaceutical interventions are needed, plus where adverse reactions are severe and increase the morbidity and mortality of patients, and there is often a limited choice of therapy (Lichter & Kurth, 1997). Conversely, pharmacogenetic testing is not likely to be economical when treating acute diseases, where many drugs are available, or where ADR's are mild. Costs to be borne by healthcare providers include the cost of genotyping, which may be significant, as well as counselling, additional clinical visits and appropriate post-test follow up (Shah, 2004). Healthcare systems could also use testing to identify especially high risk patients from ordinary at risk groups to target them for more vigorous (and more expensive) interventions in the hope of avoiding highly expensive care in the event of acute illness (Lichter & Kurth, 1997).

An example of a cost-effective pharmacogenetic test is the HER-2 test used in conjunction with Herceptin (see case study). This is because Herceptin has a high impact on the patient's quality of life and this subtype of breast cancer is very resistant to other types of therapy (Shah, 2004). Alternatively TMPT can be used in pre-prescription genotyping for children to be treated with thiopurine drugs for acute leukaemia. However the test is expensive compared to an alternative, simpler non-genetic method of red blood cell analysis (Ibid) so it has not as yet been widely adopted. Often cost effectiveness must be assessed on a case-by-case basis and depends upon a number of factors including cost of the drug and test combination, efficacy of treatment, the severity and frequency of adverse effects and the clinical setting. Many of the adverse reactions associated with CYP2D6 variants are not life threatening and so individual dose adjustment testing may not be cost effective, but new diagnostic chip technology (e.g. Roche AmpliChip), which can test for many variants at once, could change this by improving efficiency and lowering costs (Ibid.). As CYP genes are responsible for effects on many different drugs the results of a PGx test ordered for one prescription may therefore be useful when prescribing other drugs to the same patient.

3.4.5 Ethical, legal and social issues associated with pharmacogenetics

Because of the genetic profiling inherent in pharmacogenetic methods, they share many of the same ethical considerations - such as privacy, informed consent and confidentiality - as other uses of genetic tests and biomarkers (see Chapter 2). In addition, there are some additional factors, which raise ethical concerns unique to PGx.

PGx and the development and deployment of new drugs

The exclusion of particular groups from clinical trials, such as women, elderly people, children and ethnic minorities, has long been problematic (Mastroianni, Faden & Federman, 1994). Exclusion on the basis of genotype raises similar difficulties about the loss of benefits from research participation and unfair representation in the trial, and raises issues about the justice of such research (Issa, 2002). Use of PGx in designing clinical studies in order to rule out poor responders or reduce trial cohort sizes also runs the risk of skewing the results of the trial, failing to detect rare ADRs and risks statistical problems with small sample sizes. Where these methods are used it seems highly likely that PGx based drugs will have narrower and more restricted markets. This may mean that it is harder for these products to become blockbusters, with sales of over $1 billion a year. Major ethical problems are raised if new drugs will only be developed either for the most common genotypes or for groups identified as good responders. In both cases, new products might not be developed for patients with the 'wrong genotype' or for genomic groups that are too small in size to attract investment from industry. This would create new therapeutic 'orphan populations' who are economically unattractive to the pharmaceutical industry and have no access to new and more effective therapy (Rothstein & Epps 2001 and Issa, 2002). However, it should be noted that these groups, for whom an existing therapy doesn't work, already exist, but they are not currently identified. The creation of new orphan populations may therefore help public policymakers to address their unmet needs through an extension of existing policy instruments.

If patient sub-group stratification causes PGx products to be significantly more expensive than conventional medicines, this will raise issues about the distribution of access to the better treatment they offer. In the UK the National Health Service (NHS) may be unable to afford to give all patients access to these new drugs. This may lead to rationing. Similarly, developing countries may have little access to these improved therapies.

Prescribing and pharmacogenetics

It is presumed that new pharmacogenomic medicines designed to act in conjunction with a genetic test will be evaluated by regulatory bodies, jointly with this test as part of the application procedure and will be approved as a package. This has implications for the practice of 'off label' prescribing, where doctors give a drug in ways that are not listed on the drug label. In some cases this is routinely carried out, for example when prescribing to children, as it is currently rare for medicines to be tested on them. However, a small percentage of UK doctors do not currently follow drug labels carefully enough. In the well-publicised case of the inappropriate long-term use of barbiturates, this has caused very serious problems for the patients involved, including addiction and chronic illness (Medawar, 1992). The Nuffield Council on Bioethics (2003) has considered that where a drug and test are licensed together it would be unethical for a doctor to prescribe the drug without first administering the test. This is because pharmacogenetics may allow the approval of some medicines, provided they are used only in specific target groups, which would not have otherwise been approved due to possible side effects. However, if a drug and test are not part

of a joint approval, for example where tests are developed for existing products, then it may be acceptable to prescribe without using the test, depending on the risk and severity of possible ADRs. Increased training and awareness amongst prescribers, as well as new forms of post-marketing surveillance, may be required to monitor the risks of this type of medication and its prescription in particular settings.

At present many national regulatory authorities do not require evidence of a genetic test's clinical validity or utility before marketing, as their main concern has been about quality assurance to ensure reliability. However the validity and statistical relevance of certain markers can be far from certain and may vary between populations. It is therefore important to specify which populations a test has been validated in, as it may give incorrect or misleading results if applied to a non-validated population group. Clinicians and patients will need to be confident that a test gives meaningful and useful data that helps guide prescription and treatment, in order to ensure that there is a clear benefit from treatment. This is especially important if a PGx test is used as the basis to exclude a patient from treatment as a poor responder. As a consequence, the case for denying a patient therapy on the basis of a PGx test will often be a matter of professional judgement, involving the balancing of different factors, including the availability of alternative therapeutic options (Robertson, Brody, Buchannan, Kahn, & McPherson, 2002 p.157).

Inequity, stigmatisation and discrimination

In the very nature of patient and disease stratification, individuals who are profiled and assigned to a particular PGx treatment must share certain common factors in their genetic makeup. In this way, the information that a patient is on a particular medicine could inform doctors, pharmacists, and other healthcare staff about an important aspect of that individual's genotype for which the medicine is prescribed. This may reveal important information without the patient's consent (Lindpaintner, 2002 & Nuffield Council on Bioethics, 2003). In addition, some pharmacogenetic tests may give diagnostic information about other diseases, further blurring the line between pharmacogenetics and disease susceptibility testing.

A number of studies have associated specific ethnic and racial groups with adverse or non-responses to commonly used drugs because these populations have a greater frequency of a particular genetic allele. Conversely in June 2005 the drug BiDil, was approved in the US for the treatment of heart failure, specifically in the African-American population (FDA, 2005x) and was hailed in some quarters as 'the first "ethnic" drug to treat heart failure' (Kahn, 2004 p.1). However, it must be stressed that no direct link between genetics and drug response in this example has been established. There are important social risks involved in linking population groups to particular drug responses. Problems arising from these claims include the difficulty for practitioners of ascribing their patients to a particular racial or ethnic grouping (Tutton, 2004). There is also a concern that racial profiling for prescribing may be co-opted for the purposes of reinforcing discredited biological notions of race, which seek to explain social divisions and inequalities in crude genetic terms (Kahn, 2005). Such ideas have historically formed the basis of discrimination and prejudice.

Where adverse reactions are associated with particular groups, the differences in the population frequency of deleterious alleles between these socially defined groups may be statistically significant, but small in absolute size. As a consequence, only a minority of a given group may carry these alleles. Second, linking ethnic groups to particular diseases, such as Ashkenazi Jews to a higher incidence of hereditary breast cancer, may increase the stigmatisation of the group as a whole and lead to discrimination in healthcare. Great care

needs to be taken in basing prescription on crude markers of race, as the benefits of such an approach are still highly contentious.

Finally the question of insurance and genetic information is already a contentious and unresolved issue, but pharmacogenetic profiling in the context of health insurance raises some particular difficulties of its own. Assuming data from genetic testing were to be made available to health and life insurance companies, this could include an individual's response profile to certain drugs. A poor responder to a drug may then be seen as being at higher risk, and may be charged an increased premium, even if that person has a lower probability than the rest of the population of developing a given illness for which the drug is prescribed (Lindpaintner, 2002).

Commercial uncertainty and the risk of market failure

Within the pharmaceutical industry there are major concerns about the commercial implications of pharmacogenetics and the market stratification paradigm. The fear is that this will undermine the blockbuster model of a successful drug aimed at an entire patient population, and replacing it with more specific drugs aimed at patient sub-populations (Kadens & Le Gear, 2000). This might reduce the potential revenue per drug (although in theory it may also produce a greater number of successful drug products) and may also allow smaller companies to gain market share (Ibid.). There is also anxiety that new regulatory requirements to undertake PGx studies on new medicines in development may increase the regulatory hurdle, restrict product labels and make genetic testing mandatory for a much larger number of therapies.

Similarly pharmaceutical companies are unlikely to be motivated to invest in genetic tests to identify adverse drug reactions or non-responders for successful drugs already on the market, as this is likely to reduce the market for their products (Smart & Martin, 2005). A number of smaller diagnostic firms are looking to develop PGx tests for a number of important and well-established drugs (see Table 3.3), including statins, SSRIs and therapies for rheumatoid arthritis. These could offer real public health benefits, both in terms of increased patient safety and reduced prescribing costs. However, without the financial and political support of large pharmaceutical companies there is a real danger of 'market failure', with many of these potentially valuable tests never being introduced into clinical practice due to lack of resources.

3.4.6   Realising the potential of pharmacogenomics and pharmacogenetics

This chapter has reviewed the scientific, clinical and commercial development of pharmacogenomics and pharmacogenetics. The emergence of these new technologies has to be set against an ongoing productivity crisis in the pharmaceutical industry. Great hope has been placed on them to help improve both the discovery and development of new medicines. Whilst genomics has resulted in a massive increase in knowledge of basic biological processes and helped identify many more new and potentially valuable drug targets, no genomics based drug has yet to reach the market. Even Glivec, seen as one of the most promising new medicines, was based on a drug target that was characterised before the advent of the Human Genome Project. At the heart of the problem is the difficulty in turning new scientific information into clinically valid and useful knowledge. The FDA in its White Paper on innovation has called for greater investment in what it describes as the critical path of drug development, with greater focus on updating the tools currently used to assess the safety and efficacy of new medical products. However, whilst the process of 'translation' can be improved through the application of new scientific and technological approaches, it would be

a mistake to assume that this will bring quick results. By its very nature the discovery of effective new therapies, the demonstration of their safety and efficacy, and the proof of their clinical validity and utility, is a long and slow process. As a consequence, medical innovation should be seen as an incremental, rather than a revolutionary process (Nightingale & Martin, 2004).

Pharmacogenetics holds out great promise for pharmaceutical companies, clinicians, public health authorities and patients. Already a small number of products aimed at improving the prescription of established medicines are on the market. However, as highlighted above, there is a wide range of options on how the technology might be introduced, each raising different issues for the stakeholders involved. The support for, and investment in, particular options will be critical in determining what sort of applications of PGx will enter into industrial and clinical practice. The validation of gene-drug associations will not be easy and will require major investment. As a consequence, only the most commercially attractive projects, or those offering a major public health gain, will receive funding. At this point in time, it seems clear that pharmacogenetics will be applied to streamline the internal processes of creating new medicines within pharmaceutical companies (Webster *et al*, 2004). Less certain is the extent to which the same technologies will be used to improve the safety and efficacy of already licensed products, as this may not be in the commercial interests of large companies. It may therefore require significant support from government agencies and regulatory authorities to ensure that the full public health benefits of pharmacogenetics are realised. Furthermore, there are a number of important social, ethical and regulatory issues, most notably those surrounding the introduction of genetic testing more generally, that will need to be addressed before this is possible.

One of the most important consequences of the move towards pharmacogenomics and pharmacogenetics is the prospect of stratifying diseases into better-characterised sub-groups of people that are often defined in relation to drug response. The development of Glivec and other targeted small molecule cancer therapies provides some proof of principle that such an approach will work. However, it raises many important questions about the extent to which disease stratification will become a reality, as it is unclear if this will lead to drug market segmentation. Again, the commercial interests of large pharmaceutical companies will be a determining factor in the extent to which stratification become widespread. At present industry is divided on this issue, but in the longer term the characterisation of pathology at the molecular level and the development of new drugs based on genomic knowledge look certain to reframe the whole process of diagnosing and treating disease.

Chapter 4.   New biological therapies

4.1   Introduction to biologicals

Biological drugs and therapies differ in a number of ways from other pharmaceutical products. Biologicals are derived structurally and chemically from the molecular and cellular materials of the human body. This includes using genes (DNA), proteins and even whole cells as therapeutic agents. These are all naturally occurring organic molecules in contrast to traditional small molecule drugs (such as aspirin) and other types of pharmaceuticals. Biologicals are not synthetic, but may be altered, for example when cells are genetically modified. In most cases, the utility of biological therapies is related to their naturally occurring function within the human body.

Unlike other drugs, many biologicals (proteins, antibodies, therapeutic vaccines, cell therapies and most gene therapies) are not orally administered and must be injected or applied during surgical procedures. This is because DNA and proteins are broken down and destroyed if exposed to the gastric juices in the stomach. In contrast, many small molecule drugs are unaffected and can pass through the stomach lining into the bloodstream. This limitation has significant implications for the clinical use of biological therapies.

4.1.1   The development of biologicals

The practice of using biologicals as therapeutics started long before the biotechnology revolution and the advent of recombinant DNA (genetic engineering). For example, since the mid-1920s insulin extracted from cows and pigs has been used to treat diabetes. The insulin of these animals is very close in structure to that of natural human insulin. However, there have been significant difficulties with both the purification of animal derived products and allergic reactions caused by the small differences between human and non-human insulin. Other animal derived proteins, such as blood factor VIII for haemophilia (type A), have also been derived from pigs and some products are still in use.

The discovery of recombinant DNA in the 1970s ushered in the era of biotechnology. This allowed the production of proteins on an industrial scale for the first time, and without having to rely on potentially contaminated human or animal sources. It was the resulting therapeutic proteins, such as insulin, blood factor VIII and erythropoietin, which formed the first wave of new biological therapies. Biologicals have been successfully integrated into clinical practice, but their full potential has yet to be realised. Gene therapies, cell therapies, and therapeutic vaccines all need further technical development before this is possible. The impact of the Human Genome Project (HGP) has been the discovery of a large number of human genes. The function of the proteins produced by these genes is being elucidated, but at a slower pace than first hoped for. In the long term this new knowledge provides the opportunity for a greater range of biological therapies, including the possibility of new genes for use in gene therapy and novel therapeutic proteins.

4.1.2   The clinical application of biologicals

Biologicals are used mainly in secondary care and often require specialist staff and procedures for administration. Part of the benefits of biologicals is that they are novel therapies, which offer improved treatment for many chronic conditions that are poorly served by existing methods. For example, biologicals are at the forefront of much research into cancer and

diabetes. The range of applications for biological therapies, both approved and in development, covers a wide spectrum of illnesses and conditions, including CNS disorders (Alzheimer's and multiple sclerosis), growth deficiency, autoimmune diseases (rheumatoid arthritis and lupus), heart disease, skin conditions (psoriasis), digestive disorders (Crohn's disease), and infections (HIV and hepatitis C). Biological therapies also hold the possibility of treating rare inherited conditions, which are otherwise only managed by strict dietary control. For example, protein replacement therapy for Gaucher's disease can compensate for the lack of the natural proteins that patients' bodies fail to produce in this condition. In the longer term gene therapy holds the promise of a permanent cure.

4.1.3 Issues raised by the use of biological therapies

Some biological technologies raise important ethical, legal and social concerns. Gene therapy has attracted fears over the safety of participants in clinical trials and possible conflicts of interest when researchers have a financial interest in trials succeeding. Stem cell therapy has been deeply connected with ethical debates about the use of human embryos in biomedical research and wider discussions on abortion and cloning. The potential of some proposed biological therapies to offer a more personalised form of medicine, tailored to individual patients and even utilising their own cells, challenges existing regulatory regimes which are used to dealing with standardised 'off the shelf' treatments where one drug is suitable for all patients with a particular condition. Additionally, the successful implementation of novel biological therapies in clinical practice may demand the creation of new infrastructures and wider access to specialist skills and facilities. A recent example is the launch of the UK's Stem Cell Bank to assist in the ongoing process of developing medical treatments from stem cell technology. All of these factors will impact on the process of bringing new biological therapies successfully into the clinic.

Biological medicinal products, including all biotechnology-derived products are subject to regulation at both national and international level. All biotech-derived medicinal products are evaluated in the European Union (EU) through a process known as the Centralised procedure, administered by the European Medicines Agency (EMEA). The EMEA is responsible for assessing the safety and efficacy of all new drugs intended to be available on the EU market and approval, if granted, through the Centralised procedure is valid throughout all member states. In 2005 the EMEA began implementing an updated legislative framework intended to streamline some aspects of its approval process and offer incentives to smaller companies (Tsang, 2005). The changes include reduced fees when submitting products for regulatory evaluation for small-medium sized enterprises, which includes many biotech companies, and simplified administrative processes including assistance with translation into the 21 national languages of the EU. The EMEA is also introducing a greater emphasis on establishing the efficacy of new products compared to established therapies, and more stringent post market surveillance in the wake of high-profile product withdrawals such as the recall of their monoclonal antibody Natalizumab (Tysabri) for multiple sclerosis (Ibid.). In the UK the National Biological Standards Board (NBSB) is a non-departmental government body responsible for ensuring the quality and safety of biological products (NIBSC website, 2006). The NBSB acts through the National Institute for Biological Safety and Control (NIBSC), which carries out batch release safety tests on biological products for the UK market. The NIBSC also acts as an Official Medicines Control Laboratory (OMCL) for the EU, evaluating medicines for release into the European market or already released products where a safety issue such as improper storage conditions or adverse reactions arises. NIBSC is also responsible for running and housing the UK Stem Cell Bank.

The following sections will provide a brief overview of the five main groups of biological therapies (therapeutic proteins, monoclonal antibodies, therapeutic vaccines, cell therapies and gene therapies) and will describe their potential benefits, products in current use and in development, clinical use and practice issues, the ethical, legal and social concerns they raise, and the possible future development of the technology.

4.2 Therapeutic proteins

4.2.1 What are therapeutic proteins?

Proteins are one of the most common and important types of natural organic molecule in the body. They perform many roles including providing structure, storage, signalling (hormones) receptors and metabolic regulators (enzymes). Antibodies are also a type of specialised protein, but will be considered separately (see below). Proteins can act as therapeutic agents when administered to a patient because they have evolved naturally to provide a specific biological function. They are most often used therapeutically to augment a deficiency in their production by the body. For example, haemophiliacs receive blood factor (clotting) proteins and diabetics receive insulin, which they fail to produce naturally in sufficient quantity.

The development of the technology

The earliest method of obtaining proteins for medical use was to extract them directly from supplies of human or animal blood and tissue. For example, early insulins were derived from the blood of pigs. Some proteins, notably human albumin, are still collected in this way. However, this process is inefficient, cannot be easily scaled-up and suffers from the risk of infection by viruses such as HIV and hepatitis. Most proteins for therapeutic use are now produced using recombinant DNA techniques. In this process a gene for the desired protein is genetically engineered into a suitable host organism such as a bacterium, which will then express and produce that protein. These organisms can be grown in culture on an industrial scale. The first recombinant DNA product to reach the market was Eli Lilly's Humulin in 1982; this is widely seen as marking the start of the modern biotechnology era.

A number of early therapeutic proteins failed clinical trials because they were structurally altered during manufacturing, resulting in their recognition as foreign by the immune system. These problems were overcome by the more recent development of mammalian cell culture techniques, which allow proteins to be produced as closely as possible to those normally found in the human body.

Potential benefits

As proteins are naturally occurring molecules their use might be expected to avoid many of the side effects of synthetic small molecule drugs. They also perform specific biological functions and are ready-made therapies for deficiency disorders, such as diabetes. The sequencing of the human genome and the advent of proteomic technologies have massively increased the number of human proteins that can be developed as therapeutics, although the function of most of them is still unknown (Liu, 2000). As a consequence, there is great scope for the discovery of genuinely novel therapies. However, following the initial success of the first protein drugs in the 1980s it has proved much harder than expected to develop new products. In particular, significant side effects are associated with the use of cytokines and growth factors, and many proteins have failed to demonstrate sufficient efficacy in clinical trials.

4.2.2 Products currently in use or under development

There are currently over 50 different recombinant protein therapeutics available on the European and US markets. The majority of these are prescription drugs for natural protein replacement therapy. The global market for protein therapeutics in 2004 was in excess of $37 billion (see Table 4.2.1.) and represented some 8% of all medicines sold. It also constituted the fastest growing segment of the pharmaceutical market. For each class of therapeutics, market share is usually divided between two or three major companies, each with their own brand. Some markets such as insulin, are further segmented into fast acting, long lasting and alternative formulations. Recombinant protein drugs are now established as the major source of therapeutic proteins. For example, human blood Factor VIII can be extracted from blood or produced in a recombinant (genetically engineered) form, and since its launch recombinant Factor VIII has gained some 80% of the US market and accounts for around 50% of worldwide sales.

Table 4.2.1 Top-selling protein therapeutic classes in 2004.

Therapeutic protein class	Worldwide sales 2004 ($millions)
EPO (erythropoietin)	11,800
Insulin (human)	5,600
Interferon beta (IFN)	3,500
Interferon alpha (IFN)	3,200
Granulocyte Colony Stimulating Factor (G-CSF)	2,880
Human Growth Hormone (rhGH)	2,170
TNF-receptor binding protein	1,800
Blood Factor VIII	1,000
Follicle Stimulating Hormone (FSH)	950
Glucocerebridase	880
Blood Factor VIIa	750
Total sales	34,530

The majority of the most widely used therapeutic proteins are for chronic conditions poorly served by conventional therapy, including cancer, arthritis and a number of rare genetic disorders (see Table 4.2.2.). The most successful protein drug is erythropoietin with sales of over $11.8 billion in 2004 (see case study below).

A range of new therapeutic proteins are currently being developed, with some 17 in later stage (Phase II and III) clinical trials in 2004 (see Table 4.2.3.). These include treatments for cancer neurological disorders, cardiovascular diseases, autoimmune disorders and skin conditions. Despite this, only a small number of new and genuinely novel therapeutic proteins reach the market each year. In the last 20 years only 12 therapeutic proteins have been launched which had sales of over $500m a year in 2004, and only five of these were launched in the last decade (Nightingale & Martin, 2004). It therefore appears that an important protein drug is launched only every couple of years and there are few signs that this rate of innovation has increased in the last decade (FDA, 2004).

Table 4.2.3 Therapeutic proteins being developed by major companies in late stage clinical trials, 2004.

Indication	Phase II	Phase III	Total
Cardiovascular disease	1	2	3
Autoimmune disorders	2	1	3
Obesity	0	1	1
Digestive and storage diseases	0	1	1
Neurological disorders	3	0	3
Cancer and related conditions	2	0	2
Skin conditions	2	0	2
Growth deficiency	1	0	1
Reproductive health	1	0	1
			17

(Source: company web sites)

4.2.3   Clinical use and practice issues

Therapeutic proteins are already well established in the clinic and are often the best or only course of treatment in the chronic care of patients with life-long protein deficiency conditions such as diabetes, haemophilia and rare inherited conditions, such as Gaucher's disease. Many protein therapeutics do not require any specialist training or expertise beyond that needed to self-administer the drug by injection and this means that patients do not require frequent contact with physicians. Other drugs, such as IL-2, have serious side effects, can only be given by specialists and require very close monitoring.

Most protein drugs have a relatively short half-life in the body and have to be given at least once a week. This results in significant side effects, problems with patient concordance and has stimulated the development of longer-lasting products and formulations. Furthermore, many therapeutic proteins are also very expensive and may require life-long administration. For example, a course of follicle stimulating hormone cost around $2,000 (or £1,200) in 2004.

4.2.4   Realising the potential of therapeutic proteins

The main focus of the future development of therapeutic proteins is the creation of so called 'next generation' products based on protein engineering and directed evolution. This will allows specific changes to be made to the target protein in order to alter its characteristics in a beneficial way (McCafferty & Glover, 2000). Often these products involve making small changes (single amino acid substitutions) to the structure of the native protein. These methods are increasingly being used to select protein drugs whose performance in the human body is more optimal, so that they last longer, have fewer side effects and can be given less frequently.

Table 4.2.2 Details of selected protein therapeutics in use in 2005.

Protein	Trade Name	Company	Indication	Launch Date (US)	Sales in 2005 (millions)
TNF receptor binding protein	Enberel	Amgen	Inhibiting the progress of patients with moderate-severe rheumatoid arthritis.	1998	$2,600
Glucocerebrosidase	Cerezyme	Genzyme	Long term enzyme replacement for type 1 Gaucher's disease.	1994	$933
Blood Factor VIIa	NovoSeven	Novo Nordisk	Haemophilia A or B bleeding.	1993	$822
Follicle stimulating hormone	Gonal-F	Serono	Induction of ovulation in anovulatory infertility.	1997	$547
Blood Factor VIII	ReFacto	Wyeth	Haemophilia A.	2000	$268
Dnase	Pulmozyme	Genentech	Management of cystic fibrosis patients to improve pulmonary function.	1993	$222
Protein C (drotrecogin alfa)	Xigris	Eli Lilly	Treatment of sepsis.	2001	$214
Interleukin 2	Proleukin	Chiron	Metastatic kidney cancer & melanoma.	1992	$124
Granulocyte macrophage colony stimulating factor	Leukine	Berelex (Schering AG)	Acute myelogous leukaemia following chemotherapy.	1991	$72
Alpha-L-iduronidase	Aldurazyme	Biomarin/ Genzyme	Mucopolysac-charidosis I (MPS I).	2003	$77

A number of genetically altered products are already on the market and more are in late stage development. Similarly, several recombinant protein drugs, including Hoffmann-La Roche's interferon alpha (Pegasys), have been chemically modified by the attachment of a polyethylene glycol (PEG) molecule, which increases the life-span of the product in the bloodstream and reduces its likelihood of being targeted by the host immune system. Other innovations include attempts to deliver protein drugs in an aerosol in order to avoid injection. Finally, several of the most important protein therapies are shortly about to come off patent, thus opening up the possibility of cheaper 'biogenerics' (Usdin, 2002). However, regulatory agencies in Europe and the US have yet to establish the marketing approval framework for the development of these products.

In conclusion, protein therapeutics have become well established as a form of biological therapy. They offer considerable benefits over conventional small molecule drugs, especially in the treatment of some chronic conditions. The sequencing of the human genome holds the prospect of novel classes of therapy being discovered in coming decades. However, their development has proceeded more slowly than was expected in the 1980s and it has proved difficult to bring innovative new products to market. Furthermore, the fact that they are injected and are not long lasting in the body, as well as being expensive, significantly limits their use to treat serious and life-threatening conditions. The development of next generation products may start to address the clinical problems associated with their use and the introduction of biogenerics should make them more widely available.

Case study: Erythropoietin (EPO)

Erythropoietin (EPO) is a human hormone involved in stimulating the production of red blood cells (erythrocytes), which has become the most successful protein therapeutic drug. EPO regulates the rate of red cell production and is required for the survival of blood cell precursors stored in the bone marrow. The EPO protein has its own production regulated by the kidneys. Damage to the kidneys, such as that occurring in renal failure, can cause a shortage of EPO, and this in turn leads to anaemia – a deficiency of red blood cells. Anaemia can also occur after chemotherapy in cancer patients and following significant blood loss. Recombinant EPO is used to treat anaemia, increasing red blood cell counts and replacing a deficiency in the body's levels of erythropoietin.

EPO is usually administered one or more times weekly, although long-lasting formulations can reduce the dose to once every other week. In general, it takes about 10 days before any increase in the level of red blood cells can be noted. Typically for a patient receiving EPO for chemotherapy related anaemia a course of treatment will last 12-25 weeks. EPO is vital to maintain the life of patients with end-stage renal disease and kidney dialysis patients will remain on EPO for the rest of their lives. There are approximately 600,000 kidney disease patients in the US and a further 2 million with other forms of anaemia.

Treatment with EPO can reduce the need for patients to have a blood transfusion, with the associated risks of viral contamination, and shortage of donated blood. A successful treatment with EPO can also improve a patient's quality of life by stabilising mood and sleeping patterns and reversing the symptoms of anaemia such as lethargy and reduced appetite. A typical chemotherapy course with darbepoetin alfa (Aranesp from Amgen), a long lasting next generation EPO, costs around $628 (£336) per week, while pre-dialysis treatment for kidney disease costs around $175 (£99) per week with epoetin alfa (Procrit from Ortho Biologics).

4.3 Monoclonal antibodies

4.3.1 What are monoclonal antibodies?

Antibodies are proteins produced by cells of the immune system. Their function is to recognise foreign or toxic material in the body and bind to it, marking it for disposal and elimination from the body. Monoclonal antibodies (or 'MAbs') are antibodies that are structurally identical to each other and recognise a particular binding site on a specific target (or antigen). This high specificity means that monoclonal antibodies can be generated to bind particular targets involved in the pathology of a given disease and thus have considerable therapeutic potential.

The development of the technology

The first monoclonal antibodies were derived from mouse cell lines and this caused problems for the early clinical trials, as these murine antibodies were themselves foreign particles, which triggered an immune response in human patients and were rapidly eliminated. Despite this some murine monoclonal antibodies have made it to market, often with radioisotopes attached for use in medical imaging processes. Examples include arcitumomab (CEA-Scan) and nofetumomab (Verluma), which are used in tumour imaging, the most common application of the original MAbs. The next development of the technology involved using recombinant DNA techniques. Chimeric monoclonal antibodies, part mouse, part human by structure could be constructed, but these too provoked an immune response when administered to human patients. The development of 'humanised' monoclonals continued this process, as they used only the bare minimum of non-human DNA to retain the antibody's binding properties. These have generally been successful in being recognised as 'self' (i.e. not foreign) by the human immune system and have significantly fewer immunological problems when given to patients (Borrebaeck & Ohlin, 2002 and Stockwin & Holmes, 2003). It is now possible to produce fully human antibodies, which avoid most of these problems.

Potential benefits

When monoclonal antibodies were first isolated in 1975 they were heralded as a potential 'magic bullet' for treating disease. It was expected that their specificity in binding to a particular target would make them perfect drugs for targeting diseases, especially cancers, without affecting other healthy tissues or causing unwanted side-effects. However, as the first clinical trials in the 1980's revealed, harnessing the abilities of monoclonal antibodies was not as easy as had been initially thought and many early products failed during clinical testing. It has not been until very recently, with the development of 'fully humanised' monoclonal antibodies, which are well tolerated by the human immune system, that the initial promise of monoclonal antibody therapies has started to be realised (Stockwin & Holmes, 2003).

4.3.2 Products currently in use and under development

There are currently some fifteen monoclonal antibodies produced by recombinant DNA technology (chimeric, humanised and fully human) and a further ten monoclonals of murine origin on the market in the US and Europe. Some of the most well-established are shown in Table 4.3.1.

The biggest sellers, such as Remicade and Rituxan, each have annual global sales of over one billion US dollars. These are established brands (launched in the mid-1990s) and are mainly chimeric monoclonal antibodies (Rituxan) or humanised MAbs (Herceptin, Synagis). A number of fully human MAbs, such as Humira launched in 2003, are also beginning to appear

on the market, while some murine derived products (ProstaScint) remain, as they have either achieved good sales figures or established niches. In terms of diseases, most target chronic conditions, including different forms of cancer, rheumatoid arthritis, allergic asthma and suppressing graft rejection after transplantation.

The future of monoclonal antibody technology looks promising, as there are a significant number of MAbs in clinical development including new fully humanised antibodies. Table 4.3.2 below shows that there were over 60 (Phase 2 and 3) clinical trials involving monoclonal antibodies being carried out in the US during 2004. Whilst some of these trials represent testing approved MAbs for additional indications, a significant number are new products. Many monoclonal antibodies receive FDA fast-track status for US approval and generally gain regulatory approval in two years or less from the date of submission. The range of applications for monoclonal antibodies also continues to expand beyond cancer therapy, autoimmune conditions and transplant mediation, to include respiratory disorders and neurological conditions.

Table 4.3.2: Monoclonal antibodies at a significant stage of clinical development in the US, 2004.

Indication	Phase II	Phase III	Total
Cancer and related conditions	19	12	31
Autoimmune Disease	10	2	12
Digestive Disorders	3	2	5
Respiratory Disorders	3	1	4
Skin Disorders	3	0	3
Neurological Conditions	1	1	2
Other	2	0	2
Heart Disease and related conditions	0	1	1
Infectious Diseases	1	0	1
			61

(Source: PHRMA, 2004)

4.3.3   Clinical use and practice issues

Monoclonal antibodies are mainly administered in secondary care to treat patients with long term or ongoing conditions such as in cancer therapy or as part of an immunosuppressive regimen following kidney transplantation. They are therefore given in the context of specialist services, but do not require a great deal of extra knowledge or infrastructure, and in this respect are similar to many other drugs.

Monoclonal antibody therapies are also expensive. A two-dose treatment with basiliximab (Simulect from Novartis) costs approximately $3,000 (or £1,650), and MAbs must be administered by intravenous injection making them generally inappropriate for unsupervised patient use.

Table 4.3.1 Details of selected monoclonal antibodies in 2005.

Monoclonal Antibody	Trade Name	Company	Indication	Launch Date (US)	Sales in 2005 (millions)
Infliximab	Remicade	Centocor	Rheumatoid arthritis, Crohn's Disease	1998	$2,535
Rituximab	Rituxan	Genentech/ IDEC	Non-Hodgkin's lymphoma	1997	$1,989
Adalimumab	Humira	Abbott Laboratories	Rheumatoid arthritis	2002	$1,400
Palivizumab	Synagis	MedImmune	Respiratory tract viral infection	1998	$1,100
Trastuzumab	Herceptin	Genentech/Roche	Metastatic breast cancers	1998	$764
Omalizumab	Xolair	Genentech/ Tannox	Asthma	2003	$328
Efalizumab	Raptiva	Genentech	Psoriasis	2003	$94
Alemtuzumab	Campath	Millennium/ Genzyme/ Schering	Chronic lymphocytic leukaemia	2001	$75
Ibritumomab	Zevalin	Biogen-IDEC	Non-Hodgkin's lymphoma	2002	$21
Capromab pendetide	Prosta-Scint	Cytogen	Diagnostic imaging in prostate cancer	1996	$7

4.3.3   Clinical use and practice issues

Monoclonal antibodies are mainly administered in secondary care to treat patients with long term or ongoing conditions such as in cancer therapy or as part of an immunosuppressive regimen following kidney transplantation. They are therefore given in the context of specialist services, but do not require a great deal of extra knowledge or infrastructure, and in this respect are similar to many other drugs.

Monoclonal antibody therapies are also expensive. A two-dose treatment with basiliximab (Simulect from Novartis) costs approximately $3000 (or £1,650), and MAbs must be administered by intravenous injection making them generally inappropriate for unsupervised patient use.

4.3.4   Realising the potential of monoclonal antibodies

The global market for monoclonal antibodies reached an estimated $11.2 billion in 2004 and had an annual growth rate of over 40% in the five years prior to that (Research and Markets 2005). A steady stream of new products are anticipated to receive marketing approval in the next few years and the introduction of fully humanised MAbs should significantly help the development of future products. The major biotechnology companies with successful monoclonal antibody products are looking to expand applications of their already approved products and there are other companies with significant antibody pipelines which have not yet brought products to market, such as Cambridge Antibody Technology (UK) and GenMab (Denmark). In addition, new technologies and antibody engineering promise to create even greater antibody diversity and higher therapeutic specificity (Borrebaeck and Ohlin 2002: Stockwin and Holmes 2003). Despite the renewed clinical and commercial optimism surrounding MAbs, it should not be forgotten it took over 25 years from the discovery of monoclonals for them to start to realise their full potential.

Case study: Trastuzumab (Herceptin)

Trastuzumab is a monoclonal antibody produced by the US biotechnology company Genentech and marketed as Herceptin. Herceptin is a humanised (human-mouse) monoclonal antibody produced using recombinant DNA technology. Herceptin was granted regulatory approval by the US FDA in September 1998 and by the European Commission in 2000. Genentech reported worldwide Herceptin sales of $425M in 2003, of which $406M were in the U.S.

Herceptin bonds with high specificity to a human protein called HER2, which is known to be over-expressed in 25-30% of human metastatic breast cancers (Goldenberg, 1999). This over-expression causes the affected cells to be overly sensitive to the effects of growth factors, and to grow and proliferate at an elevated rate, contributing to the development of a cancerous state. Herceptin is thought to block the activity of the HER2 protein thus negating the effects of its over-expression. Herceptin binding can also target abnormal cells for destruction by the body's own immune system.

A biochemical diagnostic test is available, produced by Genentech, which identifies the subset of breast cancer patients who have amplified HER2 genes and are receptive to treatment with Herceptin.

Herceptin is approved for use as a treatment for women with metastatic breast cancers, which affect some 10% of women diagnosed with the disease. Herceptin is indicated for use on its own in women who have already had chemotherapy treatment, and for use in combination with paclitaxel (an anticancer drug produced by Bristol Myers Squibb) in women who have not had a previous course of treatment. Herceptin can reduce the size of the tumour in a patient, usually over the course of a 24-week treatment regime, but it is not a cure for metastatic breast cancer. Herceptin can significantly extend the lifespan of women suffering this type of cancer, but ultimately survival is unlikely to be increased by longer than one year.

In May 2005 at the 41st Annual meeting of the American Society of Clinical Oncology, clinical data were presented showing an application for Herceptin in the treatment of early stage (HER2-positive) breast cancer (Lancet, 2005; Genentech Press Release, 2005). Although Herceptin is not approved for treating early-stage breast cancer and indeed neither Genentech nor the drug's European suppliers Roche had submitted data for regulatory approval of this indication, the announcement created a demand amongst cancer patients for Herceptin therapy. In some countries official product approvals procedure was bypassed to make Herceptin available immediately for HER2-positive early stage breast cancer patients (Lancet, 2005). In the UK NICE targeted the drug for a fast-track assessment scheme along with four other cancer treatments, but this was criticised by some patients groups and charities as being too slow. In October 2005 two Primary Care Trusts (PCT's) in the UK were threatened with legal action for refusing to supply Herceptin to women with early-stage breast cancer although both Somerset Coast and North Stoke PCT's backed down and agreed to supply the drug before the matter went to court (Booth, 2005). Further legal challenges have followed and it has been estimated that over 100 PCT's in the UK are supplying and funding Herceptin treatment. An editorial in the Lancet (2005) criticised the sidestepping of regulatory procedures in the face of political pressure and the "misleading" interpretation of incomplete clinical data.

4.4 Therapeutic vaccines

4.4.1 What are therapeutic vaccines?

All vaccines are based on the idea of stimulating the human immune system to fight off disease. Traditional, or prophylactic vaccines, act by exposing the immune system to an inactivated form of an infectious agent such as a bacterium or virus. The immune system cells recognise a part of the infectious agent, known as an antigen, as being foreign to the body and produce antibodies which bind to the antigen and target it for destruction by other parts of the immune system. In this way if the body is then infected by a real (i.e. live) infectious agent the body has pre-prepared immune defences ready to attack the infectious agent. Therapeutic vaccines are intended to stimulate the cells of the immune system to target existing, often chronic non-infectious conditions, which have already affected the body. An example of this can be seen in the idea of cancer vaccines, which are designed to induce an immune response against tumour cells, which the immune system has previously failed to recognise as dangerous (Tsao and Carey, 2003). Other therapeutic vaccines could provide treatments for infectious diseases where there is no existing prophylactic vaccine, such as HIV and malaria. Cancer vaccines are currently the main focus of this field and will be the subject of this profile.

Potential benefits

The existing range of therapies for treating cancer, such as chemotherapy and radiotherapy often cause considerable damage to healthy tissues as well as the tumour cells they are targeting. This can cause significant, harmful and unpleasant side effects, such as post-chemotherapeutic anaemia. Furthermore, surgery to remove a tumour is not always successful, as the cancer may have become metastatic and spread to other parts of the body, and other anti-cancer drugs such as Herceptin (see case study) may only prolong patient survival for a limited time. Cancer vaccines offer a potential solution to these difficulties. By using the body's own immune system, cancer vaccines could utilise the specificity of antibodies to attack tumour cells, thus avoiding many side effects and complications (Finn, 2003; Tsao and Carey, 2003). The immune system, once activated would attack the specified tumour cells wherever they were found, thus offering a treatment for metastatic disease. In principle, cancer vaccines offer the possibility of complete patient remission.

4.4.2 Products currently in use or under development

There are currently no approved cancer vaccines on the UK or US markets, although one product (Corixa Corporation's Melacine vaccine) is licensed in Canada (Finn, 2003) – see case study. There are a variety of strategies for producing and delivering cancer vaccines. Most therapies target a specific type of cancer such as prostate or breast cancer. Some vaccines do this by presenting a neutralised whole tumour cell as the stimulating agent, much like basic prophylactic vaccines. An alternative strategy is to present a specific antigen, such as a tumour associated protein, to the immune cells in order to stimulate them. There are various methods of delivering these antigens being investigated by different companies and academic research projects, including the use of viral vectors, synthetic membranes and modified whole cells. Vaccine developers are also split between those producing 'universal' therapies, which could be applied 'off-the–shelf' to all patients suffering from a particular cancer, and 'personalised' treatments that tailor the vaccine to a specific individual's tumour cells. Table 4.4.1 below provides examples of the different types of therapeutic vaccine currently being investigated.

Table 4.4.1 Sample of therapeutic vaccines currently in development

Vaccine/ Technology	Company	Therapeutic Target	Mechanism of Action	Development Stage
BLP25 Liposomal vaccine	Biomira	Non-small cell lung cancers	Synthetic mimic of peptide widely expressed on cancer cells encased in vesicle for delivery.	Phase II clinical trials
Oncophage	Antigenics	Kidney cancer & metastatic melanoma	Personalised vaccine using heat-shock proteins derived from surgically excised tumour tissue.	Phase III clinical Trials
Insegia (G17DT)	Aphton Corp	Gastro-intestinal and gastro-esophageal cancers	Synthetic peptide mimic of natural human hormone involved in GI cancers linked to a Diphtheria toxoid to generate immune response.	Phase III clinical Trials for GI cancers & Phase II for GE cancers
Melacine	Corixa Corp	Melanoma	Lysed cells from two human melanoma cell lines with proprietary bacteria derived adjuvants.	Approved in Canada. Development suspended in US
Sipuleucel-T	Dendreon Corp	Prostate cancer	Personalised therapy. Specialised antigen-presenting cells (APC's) isolated from patient's blood, transfected with a tumour protein and re-injected.	Phase III clinical trials. FDA fast track review
Lapuleucel-T		Breast, ovarian & colon cancer		Phase I clinical trials
Prostvac-VF	Therion Biologics	Prostate cancer	Recombinant pox virus vectors express tumour associated proteins and stimulatory molecules which infect APC's to generate an immune response against tumour cells.	Phase II clinical trials
IGN101	Igeneon	Epithelial cancers	Murine monoclonal antibody that mimics protein over-expressed on epithelial cancer cells to provoke immune response.	Phase II/III
Remune	The Immune Response Corp.	HIV	Inactivated viral particles plus adjuvants. Contains core proteins of the virus so may be effective against many strains.	Phase II clinical trials

In 2004 there were 24 Phase II clinical trials and ten Phase III trials of cancer vaccines ongoing in the US (including those carried out by the US National Cancer Institute) and many more in early investigative phases (PHRMA, 2004).

4.4.3 Clinical use and practice issues

A variety of the cancer vaccine strategies being investigated raise important safety and implementation issues. The prospect of using neutralised whole tumour cells as the vaccinating agent raises concerns that the tumour cells might in some cases be reactivated and spread cancer in the patient rather than eliminating it. Similar worries surround the use of viral vectors for delivering antigens to the immune system, although the viruses used are generally genetically altered so they are no longer able to reproduce and are often from a non-human strain.

One of the biggest issues facing the field of therapeutic vaccines is the difficulty in developing a personalised vaccine. Unlike a generalised or universal cancer vaccine, which need only be developed once, they would require specialist facilities and highly trained staff to produce them on an ongoing and individual basis. In producing personalised vaccines there are major quality control and quality assurance issues both to track samples and ensure safety. Such checks would have to be performed 'on the ground' and there is uncertainty about how current regulatory regimes would adapt to this. Most importantly, it is not clear that this type of bespoke production would be economically viable or commercially attractive.

4.4.4 Realising the potential of therapeutic vaccines

The field of therapeutic vaccines has a long history, stretching back to the early years of the 20th Century (Lowy, 1997) and despite many efforts and relatively large numbers of clinical trials, relatively little success has occurred to date. In recent years there have been a number of disappointing results in large-scale Phase III clinical trials of cancer vaccines (Tsao and Carey, 2003). However, some vaccines appear to elicit a significant response in a subset of patients and have remained in development while further investigation is carried out. These technical problems have been compounded by uncertainty about the commercial and regulatory viability of the personalised vaccine strategy. In practice it may not be possible to adapt a therapy to every single cancer patient on an individual basis without incurring unfeasible expense. However, products aimed at groups of patients might receive a stimulus from Orphan Product policies. The best prospects for a workable cancer vaccine may depend on the development of products still in early stage clinical trials, as they build on new knowledge derived from the current batch of vaccine candidates. It therefore seems unlikely that many therapeutic vaccines will enter routine clinical practice in the short to medium term. Despite this lack of progress the search for a cancer vaccine that could genuinely cure forms of the disease remains one of the 'holy grails' of cancer therapeutics.

Case study: Melacine melanoma vaccine

Melacine is a therapeutic vaccine for the treatment of late stage melanoma. It was produced by Corixa Corporation and gained approval for use in Canada in 2001. Late stage melanoma, also known as malignant or metastatic melanoma is a lethal form of skin cancer. Melanoma's account for only 4% of skin cancer cases, but are responsible for some 79% of deaths attributed to skin cancer (Corixa, 2001).

The Melacine vaccine was similar to a whole tumour vaccine but consisted of lysed (broken down) components from two human melanoma-derived cell lines plus an adjuvant (Ibid.). It was an allogenic vaccine – that is the cells or cell components it used were genetically different from each other and from the patient's cells. The adjuvant is a proprietary formulation from Corixa known as DETOX, and serves to activate the body's immune system upon vaccination (Sondak and Sosman, 2003). The vaccine worked by exposing the patient's immune system to proteins and other material specific to Melacine tumour cells derived from the lysed cell lines. The cells of the immune system would then recognise the tumour cell materials as foreign and attack them wherever they were found. This helped the body to target melanoma tumour cells that have previously escaped detection by the immune system. The adjuvant material consisted partly of proteins and peptides of bacterial origin whose presence stimulated the cells of body's immune system. This is necessary because cancer patients often have suppressed immune system activity, either due to the action of tumours or other medication, and hence the body is not able to attack cancerous cells effectively (Finn, 2003).

In a number of Phase I and II clinical trials Melacine was shown to have a 10-20% response rate for stabilising or clearing some tumour sites (Ibid.). A Phase III trial, which compared Melacine to chemotherapy showed that it has similar response rates and survival levels as the chemotherapy treatment, although Melacine permitted a significantly higher patient quality of life during treatment (Finn, 2003; Sondak and Sosman, 2003). It was the results of this trial that led to the drug's approval in Canada. However, this was not sufficient evidence for the FDA to support marketing approval in the USA and they requested a further Phase III study. In 2003 Corixa restructured its operations to focus on more commercially attractive products and abandoned further development of Melacine, even though it was the first cancer vaccine in the world to be approved by a regulatory authority.

4.5   Stem cell therapy

4.5.1   What is cell therapy?

The adult human body is made up of an estimated 50 million million cells. The majority of these cells have stopped dividing and assumed a particular function, such as liver, bone, muscle or blood cells, and have adopted a fixed form to suit that purpose. It is widely believed that once cells become specialised (differentiated) they can no longer change their characteristics. However, a small sub-set of the cells in many tissues (known as stem cells) are undifferentiated and retain the ability to divide indefinitely in order to reproduce and replenish the cells that make up that tissue. The idea of cell therapy is to use these immortal stem cells (SC) to replace damaged or diseased cells and tissues in the body, in a similar fashion to traditional organ and tissue transplantation.

Embryonic stem cells (ES cells) are a unique form of stem cells found in the early embryo that can give rise to almost all the cell types in the body. These can be derived from a number of sources, including so called 'spare embryos' created during IVF procedures and embryos specifically created for research purposes. ES cells can also be created by a process known as nuclear transfer (therapeutic cloning), which involves fusing an adult cell with an altered egg cell to create an artificial 'embryo'. In contrast, adult stem cells are found in specific tissues in the adult body and only normally differentiate into a limited number of cell types. For example, haematopoietic stem cells are located in the bone marrow and can produce all the cell types that constitute the blood and immune system.

Potential benefits

Stem cell therapy has been heralded as a way to treat degenerative diseases, caused by progressive cell death or damage in particular tissues. Alzheimer's and Parkinson's diseases are caused by the loss of certain types of nerve cells (neurons) in brain tissue. Multiple Sclerosis (MS) and motor neurone disease are thought to result from damage to nerve cells, and even minor heart attacks leave areas of dead cardiac muscle which do not regenerate. At present there is no cure for these conditions and patients can only look to treatments that will alleviate the symptoms of illness. If stem cells could re-grow new neurons, replace damaged nerves and heart tissue, they would offer the real prospect of a cure for these conditions. Stem cell therapy could also work for diseases like diabetes by replacing missing or defective insulin producing cells in the pancreas, as well as providing cells for skin grafts in burns victims (McKay, 2000). Adult stem cells and those produced by therapeutic cloning hold the additional benefit that they would be recognised by the body as 'self' rather than as foreign material since they would be derived from the patient's own cells. This would avoid the complications of graft rejection, which affect transplantations where the tissue comes from a donor, and which requires the use of immunosuppressive drugs to be successful. It has even been suggested that at some point in the future, stem cells could be used to generate entire replacement organs for transplant (MRC, 2001).

In the 1990's stem cells attracted considerable attention from the biotechnology industry. Based on the success of bone marrow transplants, in which haematopoietic (blood) stem cells are transplanted, cell therapies were developed to be a part of cancer treatment. Whilst a combination of chemotherapy and cell transplant worked well for some cancers, such as lymphoma, it failed to show any clinical benefit for the more common forms of the disease, such as breast cancer (Dove, 2002). This led to a period of commercial disappointment and disinvestment, and the surviving cell therapy companies have reoriented their objectives to

focus on a wider range of therapies. These include the use of stem cells as delivery vehicles for therapeutics, and their use in cancer vaccines and tissue regeneration (Ibid.).

More recently, following significant technical advances, renewed interest has been shown in the field, with advocates claiming that stem cells are the "21st Century pill" (Fox, 2001). It has recently been shown that embryonic stem cells (ES cells) can differentiate to form a variety of cell types including heart and skeletal muscle cells, nerve cells and secretory cells (Winkler, Hescheler and Sachinidis, 2005). In addition, significant progress has been made in identifying specific biological factors that promote formation of certain cell types, although this knowledge is still at an early stage. Government funded stem cell research in the UK has also started to yield results. In 2002 the Newcastle Human Embryonic Stem Cell Group was established though a collaboration between the NHS, The University of Newcastle upon Tyne and the Centre for Life with Department of Health and Department of Trade and Industry (DTI) funding. In 2003 the Newcastle Group became one of the first two groups in the UK to derive human ES cells from spare IVF embryos and in 2005 researchers at the Centre for Life were also able to report the successful cloning of a human embryo (University of Newcastle upon Tyne Press Release, 2004; Whitfield, 2005). Another DTI funded project at Kingston University, London succeeded in producing cells with embryonic stem cell-like properties from umbilical cord blood in August 2005 (Kingston University, 2005). Developing alternative sources of stem cells such as embryos produced by therapeutic cloning or cord blood is important as it removes the need to rely on scarce material discarded from fertility treatment. In the March 2005 budget provision was made to set up the UK Stem Cell Initiative (UKSCI), a taskforce charged with producing a 10-year plan to optimise stem cell research in the UK. The UKSCI report (December, 2005) proposed increased funding over the next 10 years, increasing research co-ordination and establishing a UK public-private consortium of pharmaceutical and biotechnology companies backed by the Government to help promote stem cells as a basis for new medical treatments (Department of Health, 2005b).

4.5.2 Products currently in use or under development

The only stem cell therapy procedure currently in routine use is the isolation and transplantation of haematopoietic stem cells from the peripheral blood following chemotherapy for the treatment of leukaemia and other cancers (see case study below). Very few other potential therapies are close to introduction into the clinic as none are in phase III trials, however, a wide range are in early development (see Table 4.5.1. below) including treatments for cardiovascular disease, neurodegenerative conditions, diabetes, arthritis and a range of cancers.

One of the major technical problems facing the field is that simply applying stem cells to the target tissue in the hope of spontaneous regeneration is not a guarantee of therapeutic efficacy. As a consequence, much current effort is focused on controlling the differentiation of stem cells into specific adult cell types. For example, understanding how cultured stem cells can be programmed to turn into cardiac muscle cells for heart tissue transplants. This process is complex and involves searching for particular growth factors and manipulating the biochemical environment of the stem cells as they grow and divide. It also varies between different tissues and between embryonic and adult stem cells.

One of the major advantages of embryonic stem cells is that they are easier to grow, appear to have more potential for forming different cell types and may be able to reveal much more about the basic properties of stem cells. However, due to the major ethical issues that surround their use (see ELSI section below) there is considerable interest in developing adult

stem cells as therapies. Adult stem cells offer the advantage that they are derived from the patient and are less likely to incur graft rejection, but they are few in number and are often more difficult to access (e.g. neuronal stem cells in the brain). Furthermore, they do not survive for as long as ES cells outside the body and appear to mainly form cell types particular to their source (e.g. liver stem cells only form liver cells). There has been some suggestion that certain adult stem cell types (e.g. haematopoietic and muscle stem cells) can be induced to differentiate into a range of other tissues, but this has yet to be conclusively demonstrated. Embryonic stem cells can be 'created' by therapeutic cloning methods, but this technology is still relatively new and hard to control precisely. There are also significant ethical issues associated with its use.

A third type of stem cell can be harvested from the blood taken from the umbilical cord when a baby is born. Umbilical cord blood stem cells are now used as an alternative to haematopoietic stem cells derived from bone marrow or peripheral blood in operations for a variety of blood cell disorders, including leukaemia (Rocha, Sanz, and Gluckman, 2004). Already a number of centres and firms have been established to bank cord blood, so that it can be used as a therapy should that individual develop a blood cell cancer in later life.

Researchers are also hoping to find the growth factors (similar to G-CSF) that control the mobilisation, division and differentiation of stem cells into various tissue types. This would allow stem cells to be collected and modified more easily, and might lead to the creation of drugs that would activate stem cells without having to remove them from the body.

4.5.3   Clinical use and practice issues

The use of haematopoietic stem cells provides the only established model for how stem cells might be used more generally (see case study). This application involves highly specialist staff and equipment and is currently restricted to tertiary care. In this type of autologous therapy (i.e. using the patient's own stem cells), cells are processed on an individual basis. This requires complex cell separation and purification equipment, and sterile facilities capable of operating at a very high standard to avoid infection. Whilst these procedures are starting to become routine, they are still expensive and demand significant infrastructure and expertise.

Unlike the use of therapeutic proteins and monoclonal antibodies, stem cell therapy may only need to be applied on a limited number of occasions. However, they would generally require surgical procedures similar to current tissue transplantation. The stem cell transplant would also need a period of outpatient monitoring to ensure the new cells are successfully engrafted following the treatment.

In the longer term, researchers and companies are looking to develop alternative strategies other than simply reimplanting tissue-restricted cells back into the body. Several approaches are being investigated including the creation of 'universal' allogenic cell lines, which could be transplanted into a wide range of patients. These would be highly characterised and standardised cell lines similar to other types of biological drug and would avoid the need for local cell processing, as they could be simply injected or transplanted into the patient.

Table 4.5.1   A selection of commercial cell therapy projects currently in development.

Name	Company	Therapeutic Target	Mechanism of Action	Development Stage
MyoCell	BioHeart	Cardiovascular diseases (heart attack & end-stage heart disease)	Adult stem cells from skeletal muscle implanted into damaged heart tissue during surgery.	Phase I/II clinical trials in Europe, Phase I trials in the US
Human ES cells	Geron Corporation	Restoration of damaged organ function	Differentiation of embryonic stem cells into neural, heart, pancreas, bone and blood cells.	Animal model testing
Prochymal	Osiris Therapeutics	Combating Graft-Versus-Host Disease (GVHD) in bone marrow transplantation.	he active ingredient of Prochymal is adult Mesenchymal Stem Cells (MSCs). MSCs move to damaged areas of the body where they interact with immune cells to reduce inflammation and assist in tissue repair..	Phase II clinical trials
ReN004	ReNeuron	Parkinson's disease	ReN004 is a stem cell line that can be induced to produce functional dopamine-producing neurons to replace damages neural cells.	ReN004 is being re-derived to GLP standards ahead of pre-clinical efficacy testing.
CB001	Viacell	Bone marrow transplantation	Concentrated and purified haematopoietic stem cells will accelerate repopulation of immune system following transplant.	Phase I
StemEx	Gamida-Cell	Haematological malignancies	Stem cells derived from human umbilical cord blood grown externally and used in bone marrow transplant indications.	Phase I/II clinical trials
Regen-Immune	Cytomatrix	Infections, cancer	Growth of T-cells from blood stem cells.	Phase 1 trials scheduled to commence in 2006

However, the regulatory framework governing the manufacture and use of all types of stem cell products is still emerging (Weber, 2004). In the US the FDA does not directly regulate many conventional surgical procedures, such as bone marrow transplantation, but closely controls both the devices used in cell processing and the procedures used to store and manipulate cells in order to prevent infection. It remains to be seen exactly how the regulatory framework will influence the types of stem cell therapies that ultimately become available.

4.5.4 Ethical, legal and social issues

Stem cell research has been surrounded by controversy, mainly because of the use of embryonic stem (ES) cells. In particular, there continues to be a major social and ethical debate about the morality of using embryos in scientific research, with many anti-abortion groups objecting to the use of unused or so-called spare embryos created during IVF infertility treatment. Current UK legislation allows spare embryos from fertility clinics to be utilised in stem cell research until 14 days after creation, at which point they must be destroyed. It is not presently permissible to create new embryos purely for research purposes. However, therapeutic cloning, which involves fusing an adult and egg cell to create embryonic stem cells, is permissible. This is also controversial, as ES cells have remarkable properties and can themselves be used to create new embryos, completely bypassing the need for sexual reproduction. Opponents of the use of embryonic stem cells cite the existence of adult stem cells as a less controversial alternative, but it remains to be seen whether adult SC's retain sufficient developmental potential to generate effective therapies.

Under current UK law the Human Fertilisation and Embryology Authority (HFEA) is responsible for controlling and approving the creation and use in research of all embryos up until the 14-day limit. Initially, the HFEA's remit mainly concerned research on spare embryos, but in 2001 in response to technological advances the UK parliament extended legislation to allow research on cells derived from human embryos for the purposes of increasing knowledge of embryonic development, treatment of serious disease and application of this knowledge. In the same year, following a House of Lords Select Committee report, the Human Cloning Act came into force, prohibiting the practice of, or attempt at, reproductive cloning (i.e. creating cloned humans). This was intended as a safeguard to allow the continued use of the technique of therapeutic cloning to create embryos from ES cells for research purposes. Therapeutic cloning has the potential to use an individual's own body cells to produce an embryo which will have the same genetic make-up as that individual. ES cells derived from that embryo could then potentially be used to repair damaged tissue in the individual with no danger of graft rejection. However, it does necessitate creation of new embryos and ES cells. As a consequence, it is illegal to generate or work with new embryonic stem cells without a license from the HFEA, and each research application is considered separately. Research in this area is therefore very highly regulated.

In the US it is forbidden to use federal funding for research that would create new embryonic stem cells, and researchers can only work with an approved list of ES cell lines established before the August 2001 ban (Knight, 2004). In response, there have been a number of concerns raised by the scientific establishment, as many of the most promising stem cell lines were created after the ban and many older cell lines have been contaminated by cultivation in conjunction with mouse cells (Aldhous, 2005). Although there has been some political movement on the issue of stem cell funding (Check, 2005; Herrera, 2005) the ban remains in place. However, the ban on federal funding does not preclude ES cell research funded from other sources and in November 2004 the State of California passed the *California Stem Cell Research and Cures Initiative*, also known as Proposition 71 (Knight, 2004). This bill allows

the sale of bonds to raise non-federal money to provide a planned $3 billion in funding for stem cell research within the state, beginning with the creation of a California Institute for Regenerative Medicine (CIRM) which will oversee distribution of the rest of the funding. Since the proposition was passed the distribution of the funding has been hampered by a series of legal challenges to the CIRM by opponents of stem cell research. Although none have yet been successful, they have delayed the project. A number of other states including New Jersey, Connecticut, Wisconsin and Massachusetts have all begun moves towards providing their own state funding programmes (Aldhous, 2005; Herrera, 2005).

In contrast, the situation in continental Europe is one of plurality, with different countries favouring a range of approaches to ethical issues and choosing a diversity of legislation. There have been some generally agreed principles, such as a prohibition on attempting human reproductive cloning and germ line gene therapy (human genetic engineering). However, the issue of using embryonic stem cells has provoked a long and heated debate in the European Union (EU). The Council of Europe's 1999 convention on 'Human Rights and Biomedicine' allows different countries to decide for themselves whether or not to allow embryo research using spare embryos generated during fertility treatment, but prohibits the specific creation of embryos for research (Lenoir, 2000). As of January 2006 there was still no specific EU legislation on ES cells, and there had been no impetus to harmonise national regulations to an international standard. As a result of this lack of consensus, controversy has arisen over the question of EU funding for stem cell research. In particular, ethical debate has centred on therapeutic cloning which does not involve a fertilised egg, but creates ES cells that can in turn be used to create new embryos specifically for research processes.

In November 2003 the European Parliament voted to allow funding for research on newly created embryos (Scott, 2003), but a month later the EU research ministers failed to reach a conclusive decision on the matter. In effect this has left the European Commission free to accept and inspect bids for funding for research involving therapeutic cloning techniques on an individual case-by-case basis (Abbott, 2003).

4.5.5 Realising the potential of stem cells

At present the central difficulty in bringing stem cell therapy into clinical use is understanding and controlling the mechanisms of cell differentiation. As can be seen from the commercial projects in development, this work is still at a relatively early stage. The use of peripheral blood stem cells is successful largely because the cells are returned to a native environment in which they would normally proliferate and differentiate. Furthermore, this builds on nearly 50 years of experience and experimentation with bone marrow transplantation. This will be harder to replicate in other tissues and will not happen quickly. Research efforts are still divided between work on embryonic and adult stem cells, and despite the ethical and political controversy surrounding this research, the use of ES cells may be needed to understand some of the basic processes of cell differentiation. To date the most promising lines of enquiry appear to lie where adult stem cells are extracted and multiplied to replace tissue types identical or very similar to their source.

Cell therapy therefore remains a promising long-term prospect for medical treatment of currently incurable conditions, but there are significant technical problems to be overcome before this can occur. It is therefore unlikely to be a clinical option beyond its established use in cancer treatment in the near future.

Case study: Haematopoietic stem cells in cancer therapy

Haematopoietic stem cells (HSC) are mainly found in the bone marrow and in very small numbers in circulating peripheral blood. They are adult stem cells that give rise to all the cell types of the blood and immune system, including red blood cells for carrying oxygen, white blood cells of the immune system and platelets, which allow blood to clot. They are the largest population of stem cells in the adult body.

The treatment of certain types of cancers of the blood and immune system, including leukaemia, lymphoma and myeloma involves high dose chemotherapy and radiation therapy. These treatments aim to destroy rapidly dividing cells, as this is a major characteristic of most tumours. HSC's are also rapidly dividing and are therefore also affected by this sort of cancer therapy. Without healthy bone marrow (i.e. a healthy HSC population) the body is not able to make enough blood and immune cells to supply oxygen and fight off infection. As a consequence high dose chemotherapy is a life-threatening intervention.

The aim of traditional bone marrow transplantation (BMT) is to remove a patient's bone marrow before chemotherapy and then reimplant it after treatment in the hope that the cancer cells will have been destroyed and that a healthy population of HSCs can be replenished. Alternatively, the marrow from a matched donor can be reimplanted, avoiding the risk of cancer cells being inadvertently returned to the body. Recently it has been found that the drug G-CSF can mobilise HSCs and greatly increase their number in the peripheral blood. It has therefore become possible to use this technique as a means of directly harvesting HSCs, thus avoiding the need for invasive surgery. In 2001 there were 16,700 HSC transplants of this sort in Europe and 2,100 in the UK. Autologous transplants occur when a patient is able to receive their own stem cells, removed before the cancer treatment has occurred. This procedure requires the patient's blood to be processed (filtered) to obtain the peripheral blood stem cells and treated to remove any cancer cells. In allogeneic transplants the patient receives stem cells from a closely matched donor (often a relative), and may need imunosuppressive treatment to prevent graft versus host complications.

The transplantation of HSCs is often used to treat cancers in remission, or recurrent cancers that have not responded to other treatment. The transplanted stem cells usually lodge in the bone marrow and begin producing new blood cells within 2 - 4 weeks, although the complete reconstitution of the immune system can take from several months to two years. As HSC transplantation is a surgical procedure and not a product in itself it is not owned by any commercial entity. However, the drug G-CSF is proprietorial and the procedure as a whole is expensive.

4.6   Gene Therapy

4.6.1   What is gene therapy?

There are two broad types of gene therapy, somatic and germ line. Somatic gene therapy can be defined simply as the delivery of functional genes to somatic tissue for the treatment of disease. Here a therapeutic gene is administered to the patient in order to make changes to the somatic cells in the body, but not to the germ cells (sperm and eggs), which are involved in reproduction. The therapy therefore only affects the person to whom it is given.

In contrast germ line gene therapy is aimed at genetically altering germ cells for the treatment of diseases in future generations. Here the therapeutic gene is inherited by the offspring of the treated individual and becomes a stable part of their genetic make-up. For both ethical and safety reasons, germ line therapy is not being developed in humans at present.

Gene therapies are based on clinical interventions at a molecular level. Advances in genetics and molecular biology have led to an understanding of many of the fundamental events, which are responsible for disease pathology. These can be broadly categorised into two groups; genetic or acquired. In a genetic disease, the underlying molecular cause is some form of inherited genetic abnormality (mutation, deletion, translocation) in a gene that codes for a key protein. For example, in the case of cystic fibrosis (CF) the CFTR gene is altered and leads to the build-up of mucus in the lungs. In an acquired disease, errors in the DNA are caused by environmental factors or the ageing process, which may result in local genetic alterations or changes in the pattern of normal gene expression in some tissues. For example, in many cancers key genes that regulate normal cell growth, termed cellular oncogenes, are altered locally and this leads to tumour formation. Other diseases are caused by the up-or down-regulation of a particular gene, which leads to an excess or shortage of important proteins. In principle, almost any disease can be described at the molecular level. Many strategies for gene therapy attempt to either correct or compensate for these underlying errors, or enhance normal biological processes, such as the immune response, to combat disease.

When a gene is transferred into the patient it will be 'expressed', just like the body's natural DNA, and produce a protein. This expressed protein can act as a therapeutic in a number of ways, including restoring a function lost as a result of an inborn genetic error (e.g. inserting the gene for Blood Factor VIII to treat haemophilia), or producing a novel function (e.g. inserting a cytokine gene into a tumour in order to stimulate an immune response against the cancer cells). Many gene therapy applications can be thought of as another means of delivering protein drugs locally or systemically, although they go beyond the use of the established therapeutic proteins described earlier.

Potential benefits

Gene therapy has been heralded as having the potential to be one of the most important developments in medicine in the next century. It is best thought of as a family of technologies resulting from the application of gene transfer techniques to clinical problems. These methods have been successfully applied to many tissues in model systems and are under investigation in a wide range of human diseases. Therapeutic interventions using gene transfer may become increasingly feasible as definitive information accumulates about the human genome, leading to the identification of genes involved in common diseases and a better understanding of the molecular processes of pathology. In principle, gene therapies could be highly targeted, have fewer side effects and be applied to a number of important chronic

diseases that are poorly served at present. More importantly, in the long-term gene therapy holds out the promise of a permanent cure for a number of genetic diseases, as it may be able to correct the underlying cause of these conditions through the process of gene replacement. However, in the short-term at least, it is likely to be limited to the treatment of a relatively small number of rare inherited conditions, HIV infection and different forms of cancer. Of these, the latter is the most promising.

4.6.2   Products currently in use or under development

All gene therapies have at their core three distinct elements: A) *the therapeutic gene* – which contains the information required to make the relevant protein; B) *an expression system* - this consists of DNA sequences which flank the therapeutic gene and control when and in what tissues or cells it can be activated; C) *a delivery system or vector* - in order to enter the body, avoid degradation and be targeted to the desired site in the body (cell type), the expression system must be contained in a vector.

Delivery systems can be divided into two groups:

Viral vectors - these have the advantage of being biologically specific, i.e. they only infect particular cell types, are able to enter and be expressed in cells easily, and can be manipulated to carry a therapeutic payload. However, there are a number of significant safety concerns associated with the use of these potentially infectious agents.

Non-viral delivery systems - have been more difficult to design, as they are not biologically specific to a given cell type and do not as readily enter cells in the body. In this sense they have to be guided physically or biologically to the target site. However, they have few of the safety problems associated with viral vectors.

In the 1,000+ clinical trails conducted by the start of 2006 viral vectors have been the dominant technology, being used in over 60% of all clinical studies. In particular, some 49% of trials have used either a modified retrovirus (like the HIV virus) or an adenovirus. The viral particles are genetically modified to neutralise their harmful and replicative potential, and refitted with the desired human gene(s). Alternative non-viral methods of gene delivery have been used in 25% of clinical trials and involve either the use of a lipid (fat-like) coating, which can protect the DNA and deliver it through the cell wall, or the local injection of naked DNA to the target tissue (Wiley, 2006).

Furthermore, there are two distinct ways in which these gene transfer methods can be applied:

Ex vivo **gene therapy** - is where the modification of the patient's cells occurs outside the body. In *ex vivo* therapies cells are removed, genetically altered in culture and returned to the patient, for example by blood transfusion or bone marrow transplantation.

In vivo **gene therapy** - is where the genetic alteration of the cells occurs by direct administration of the therapy to the patient. *In vivo* therapies are mainly given by injection.

Ex vivo therapy requires more intensive laboratory and cell processing procedures, but is a generally easier means of undertaking efficient gene transfer. In contrast, *in vivo* therapy is more demanding as it involves targeting the therapeutic gene to a specific site in the body. However, *in vivo* methods are more clinically and commercially attractive, as they are easier to manufacture and use in practice.

The first officially sanctioned clinical trial of gene therapy was carried out in the US in 1990 for the treatment of a rare genetic disease. According to the Wiley database of Gene Therapy Clinical Trials Worldwide (Wiley, 2006), the US has organised the majority (65%) of the 1,145 gene therapy trials that have taken place, with the UK being the second most active country, organising 134 trials (12% of the total). In terms of disease focus, two-thirds of the gene therapy clinical trials that have been carried out have involved investigative therapies for cancer. In part, this is because it has been easier to get regulatory approval for cancer gene therapy trials than for any other applications. Other targets have included monogenic disorders (9% of all trials), vascular disease (9%), and infectious diseases such as HIV (7%). Experimental therapies are also being developed for a range of other diseases, including Alzheimer's, vascular disease and arthritis. Examples of these are given in Table 4.6.1.

Overall, there has been a great deal of clinical interest in gene therapy and the fist successful cure was announced in 2000 following *ex vivo* therapy in a small number of children suffering from a very rare genetic disorder, X-linked severe combined immune deficiency (X-SCID) (Leonard, 2000). Altogether, 160 Phase II trials have been undertaken since 1989. However, only 24 of these made it into Phase III (2.1% of the total). Of the 10 Phase III trials that appeared to be ongoing in January 2006 (Wiley, 2006), one was for peripheral arterial disease, two were for HIV infection and seven were for cancer (one of which were using the p53 gene – see case study). In cancer gene therapy the preferred method of attacking tumours has been to either transfer genes, mainly cytokines (e.g. GM-CSF), which induce the immune system to attack cancer cells (in effect a form of cancer vaccine) or to use tumour a suppressor gene, such as p53, to stop cell division (Lo, Day and Hung, 2005). Only one gene therapy product has been successfully brought to market. This is a treatment for head and neck cancer using the p53 gene, which is only approved and distributed in China (see Gendicine case study).

4.6.3   Clinical use and practice issues

The main focus of gene therapy research involves direct *in vivo* gene applications. However, unlike the use of standard injectable drugs, gene therapy vectors often require localised delivery to specific tissues or tumour sites. As a consequence, this demands specialised personnel to administer the treatment, which is almost always carried out in a hospital setting. This is particularly true when gene therapy is given as an adjuvant to conventional treatments, such as surgery or chemotherapy. The same is true for *ex vivo* therapies involving cell extraction and modification. These procedures require intensive laboratory work as well as specialised cell processing equipment and facilities, making them expensive and commercially unattractive.

4.6.4   Ethical, legal and social issues

Gene therapy can be thought of as a form of human genetic engineering and often involves testing highly experimental treatments and novel practices in human subjects. The prospect of developing a successful gene therapy has held great allure for pioneering researchers. However, the race to be the first person to make it work, as well as the very significant financial interests involved, has led to a series of scandals. As a consequence it has become one of the most controversial areas of modern medicine.

Table 4.6.1 Examples of commercial gene therapy projects currently in development.

Name	Company	Therapeutic Target	Mechanism of Action	Development Stage
MyoDys	Transgene	Muscular dystrophy	Plasmid carrying human dystropin gene and selective promoters to ensure the gene is expressed only in muscle tissue.	Phase I clinical trials completed
Allovectin-7	Vical	Late stage melanoma tumours	Lipid-enclosed plasmid with selected genes to trigger an inflammatory immune response.	Phase II clinical trials completed
CERE-110	Ceregene	Mild to moderate Alzheimer's Disease	Delivery of Nerve Growth Factor (NGF) to brain regions using whole cell and viral vectors.	Phase I clinical trials completed
BioBypass	GenVec	Peripheral Vascular Disease	Adenovirus vector to deliver the gene for vascular endothelial growth factor (VEGF) to leg tissues to enable growth of new blood vessels.	Phase II clinical trials
tgAAC94	Targeted Genetics	Inflammatory Arthritis	Adeno Associated Virus (AAV) vector designed to deliver a DNA sequence encoding a potent inhibitor of tumour necrosis factor alpha (TNF-alpha), a key mediator of inflammation.	Phase I clinical trials.
VRX496	VirxSys	HIV infection	Modified lentivirus carrying genes which prevent HIV replication.	Phase I clinical trial
HIF gene	Genzyme	Peripheral arterial disease, adjunct to heart bypass surgery	Administration of the HIF-1α gene, which responds to low oxygen levels (due to poor blood supply) to induce growth of new blood vessels.	Phase I clinical trials
MetXia	Oxford BioMedica	Breast, head and neck, ovarian, liver and pancreatic cancers	Pro-drug activation using retroviral vector in conjunction with chemotherapy.	Phase I/II clinical trials for breast and pancreatic cancers

In 1980 Professor Martin Cline provoked international outrage when he deliberately went ahead with the first use of recombinant DNA technology in humans after the experimental protocol had been refused ethical approval in the US. Following the Cline debacle and a US President's Commission Inquiry into the ethics of gene therapy, the US established strict oversight of the field under the auspices of the NIH's Recombinant DNA Advisory Committee (RAC). A similar body, the Gene Therapy Advisory Committee (GTAC), was established in the UK in the 1990s. Despite the tight regulation of the design of vectors and experimental procedures, more recently there have been other major setbacks for the field. In 1999 a teenage patient, Jesse Gelsinger, died after suffering a severe immune response to the viral vector used in a gene therapy trial for a rare genetic condition at the University of Pennsylvania. The subsequent investigation showed that safety protocols had not been accurately followed by the researchers conducting the trial, and that significant adverse reactions in other patients and monkeys had not been reported to the FDA. This led the Agency to suspend all gene therapy research at the University, as well as a number of other clinical studies involving the same adenoviral vector system until further risk assessment could be carried out. This episode led to more stringent safety protocols for gene therapy trials internationally and a loss of public and investor confidence in the field. In 1999 some 116 gene therapy clinical trials were instigated internationally, however, by 2005 that number had fallen to 77 and many of the companies working on the technology had disinvested.

Significant safety problems have also found to be associated with the use of the other main (retroviral) vector system. In 2002 it was revealed that two of the nine French children who had by then been successfully cured of X-SCID using gene therapy had developed leukaemia as a result of the retroviral vector damaging their DNA. The trials were called to a halt, as were similar projects in the US. Furthermore, in 2004 significant safety concerns were raised in the UK about the safety of the third (lentiviral) vector system.

4.6.5   Realising the potential of gene therapy

Gene therapy still remains at an early stage of development, despite over 1,000 clinical trials taking place since 1990. Some notably successes have been achieved; genes have been transferred into many tissues in the human body, viable strategies have been created to tackle a number of important diseases, and the concept has been proven to work in two areas (SCID and p53 cancer therapy). However, the very serious safety problems that have arisen in recent years cast a long shadow over the future of the field. Furthermore, gene transfer systems still remain very inefficient and in most cases are not suitable for routine clinical application. As a result of the serious safety problems described above, the use of the most efficient viral vectors has been called into question. At the same time, non-viral vectors such as plasmids, lipid coatings and gene-associated targeting proteins have generally been found to show poor performance in both gene delivery and the sustainability of therapeutic response. It therefore appears that despite its long term potential, further advances in gene therapy may have to wait until there is a better understanding of the safety problems associated with gene transfer and a new generation of vector systems has been developed.

Case study: Gendicine – gene therapy for head and neck cancer

In October 2003 the Chinese State Food and Drug Regulation Agency approved the world's first gene therapy product, Gendicine, for commercial manufacture. Produced by Chinese biotech firm Shenzhen SiBiono GenTech, it is a treatment for a type of cancer known as head and neck squamous cell carcinoma (HNSCC), which accounts for some 10% of new cancer cases per year in China (Pearson, Jia and Kandachi, 2004).

Gendicine uses an adenoviral vector to deliver the normal human form of a gene known as p53 to cancerous cells. P53 is a tumour suppressor gene that is normally expressed at very low levels in healthy cells, but becomes activated when the cell's DNA becomes damaged. In 50-70% of cancers the p53 gene is found to be deleted or mutated (BIOPHARM International, 2004). Mutant forms of p53 not only fail to halt cell proliferation, but can also induce resistance to chemotherapy drugs. When the normal or 'wildtype' p53 is delivered into tumour cells the presence of damaged DNA causes it to be expressed at greater than normal levels. The resulting protein has a number of anti-tumour effects as it can halt the cells reproductive cycle, instigate cell death, stimulate the cells of the body's immune system to attack the tumour cells and also reduce the expression of growth factor and drug resistance genes (BIOPHARM International, 2004).

Gendicine is designed to be administered by injection either locally at tumour sites or systemically. In joint clinical trials with radiotherapy and weekly gene therapy injections, 64% of late stage HNSCC tumours showed complete regression and 32% showed a partial regression (Pearson, Jia and Kandachi, 2004). There is also anecdotal evidence that combination therapy with Gendicine relieves some of the discomfort associated with chemotherapy and radiotherapy treatments (BIOPHARM International, 2004).

The adenovirus used to deliver the p53 gene is incapable of replication, so it cannot itself infect the patient's body or cause viral damage to cells. In addition, the p53 gene it delivers is not incorporated into the host cell's DNA, removing both the danger of insertional mutagenesis seen with X-SCID gene therapy. Although the virus will insert the gene into some health cells around the tumour site, the p53 will not be activated here because there is no DNA damage, so reducing the side-effects of treatment. To date the main side-effect reported with the treatment is a limited fever (Pearson, Jia and Kandachi, 2004).

Gendicine has been investigated in further clinical trials to treat a variety of other cancers including liver, lung, thyroid, pancreas, intestine and breast cancer and a number of US firms, such as Introgen, are currently working on similar gene therapy products.

Chapter 5. The changing context of medicines development and use

A number of major changes are occurring in the broad environment surrounding the development and use of new drugs and diagnostics. These include changes in the structure of the pharmaceutical industry and the supply of new medicines; market structure and demand; government health policy and the organisation of the NHS; professional practice; and the regulation of new medical technologies. In addition, the UK government has taken a number of initiatives to promote the development of genomic medicine. The main changes and new policy initiatives likely to affect the development, licensing, marketing, distribution, and use of new medical technologies will be briefly described below. The final section will then summarise the changes most likely to influence the development and diffusion of the genomic technologies described in Chapters 2-4.

5.1   The changing pharmaceutical industry

5.1.1   Challenges facing the industry

The pharmaceutical sector is one of the most important to the UK economy in terms of size, employment, profitability and export earnings. According to the Association of the British Pharmaceutical Industry the sector employed around 180,000 people and generated a trade surplus of £3.6 billion in 2003. The dominant pattern of innovation within the mainstream pharmaceutical industry arose during the 1940s and 1950s, following the discovery of antibiotics and sulfa drugs, and was one of chemistry-based drug discovery. This exploited naturally occurring biologically active compounds and random screening of chemical libraries to produce small molecule drugs. In the post-war period the industry became increasingly research-based, invested heavily in R&D and built large in-house research capabilities in synthetic organic chemistry. While this drug discovery paradigm was successful during the Golden Age of the pharmaceutical industry in the 1950s and 1960s, by the 1970s and 1980s decreasing returns had set in and there was a slowdown in the production of novel therapeutics.

Following the birth of recombinant DNA in the 1970s, a series of biology and genetics-based technologies have opened up new possibilities for the creation of novel biological therapies and diagnostics. These technologies emerged in a series of 'waves' during the 1980s and 1990s, forming the basis for the creation of some 3,000 new biotechnology firms in Europe and North America. Whilst there has been a steady growth in the number of biological drugs approved for marketing, until recently genetic technologies have had little impact on the central process of creating new small molecule drugs. Only with the advent of a new cluster of technologies centred on the use of gene sequence and expression information have major changes occurred. The establishment of the Human Genome Project in 1990 marked the start of the development of genomics on a large scale and was quickly followed by the creation of the first generation of genomics firms exploiting high speed sequencing technologies to identify genes. In the last few years there has been a massive expansion in the amount and types of genomic data available. The potential of these new technologies to improve the likelihood of therapeutic success has driven all major pharmaceutical companies to embrace genomics and has seen their reinvention from predominantly chemistry-based firms to enterprises led by the life sciences.

Over the last two decades the industry has faced a number of important challenges, including:

- **Globalisation and international harmonisation** – The liberalisation of international trade has led to a greater emphasis on the harmonisation of drug regulations and the creation of integrated markets, as in the European Union. These trends are creating new opportunities for the global pharmaceutical industry to expand markets and relocate manufacturing;

- **Healthcare cost containment** – Many western governments are facing rapidly rising healthcare costs and have introduced policies to control public expenditure through measures such as managed care programmes. Drugs budgets have also grown quickly in the last decade, with NHS expenditure on medicines rising from £3.7 billion in 1992 to over £8.0 billion in 2002, and have become the focus on a number of technology assessment and cost containment initiatives. This is placing increasing pressure on companies to demonstrate the cost-effectiveness of new medicines. Recently, following the Wanless review, greater emphasis has been placed on increasing appropriate prescribing in order to decrease other healthcare costs i.e. seeing drug therapy in terms of prevention. As a consequence, the projected post Wanless growth in prescribing is projected to be 8% per annum;

- **An ageing population in the core markets of North America and Europe** – The percentage of people over 65 in the UK has doubled from around 8% in the 1940s to 16% by the 1990s. The main causes of death in the UK are now chronic degenerative conditions, such as cancer and heart disease;

Diagram 5.1 Decreasing R&D productivity

New Drug Applications VS R&D Investment 1970-2000
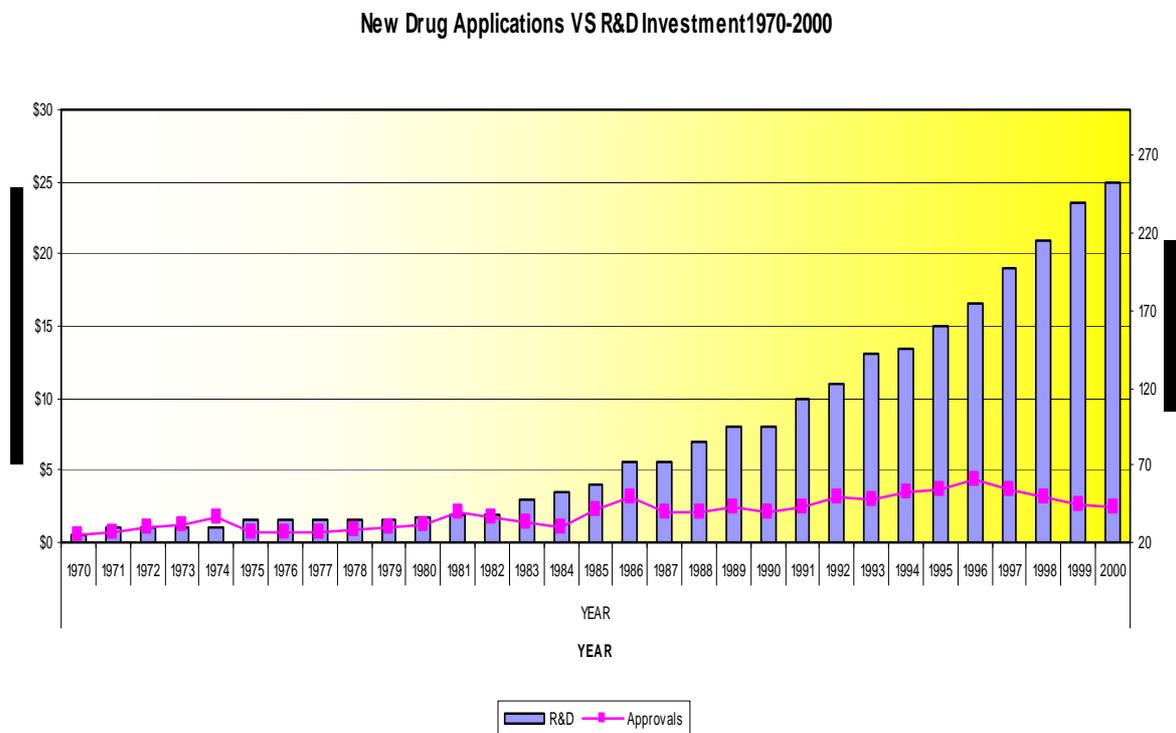
- **Patent expiries and the growth of generics** – A number of the most commercially important blockbuster drugs have come off patent in recent years and more are set to expire in the near future. In addition, there has been a steady growth in the availability and use of unbranded generic medicines (i.e. drugs that are no longer covered by patents). Both these trends threaten the profitability of leading companies;

- **Decreasing R&D productivity** – Despite a very significant increase in R&D expenditure since the 1970s, the number of new drugs approved for marketing in the USA by the FDA has hardly risen in the last 20 years (see Diagram 5.1. above). This is reflected in the increasing cost of bringing a new drug to market, which now stands at roughly $900m and has increased five-fold since the 1970s. This productivity crisis has resulted in a number of leading firms facing increasingly empty drug pipelines;

- **The rise of biotechnology** – The dramatic growth of the biological sciences since the 1980s has created new knowledge of the workings of the human body and disease pathology. This has opened up important new possibilities for the creation of novel medicines, but has required a major change in the knowledge base and core competencies of the industry.

5.1.2   The changing face of the pharmaceutical sector

In response to these challenges a number of important changes have occurred in the pharmaceutical sector, including:

- **Industry consolidation** – There has been a series of mergers and acquisitions between leading firms over the last decade. This has been driven by the need to access new markets by extending geographical reach, to broaden drug pipelines and product portfolios, and gain economies of scale in sales and marketing. As a consequence, the market share of the top 10 companies had grown from 30% to over 48% by 2002 and their sales had increased from $52 billion to $187 billion in the same period;

- **Changing product focus** – The changing demographic of the industry's core markets is leading to greater emphasis on the management of chronic diseases, including cancer, cardiovascular disease, arthritis and neuro-degenerative conditions such as Alzheimer's. Many of these are poorly served by existing therapies. There is also a trend towards the development of medicines that can be used to treat people at risk of serious disease before they become symptomatic (e.g. statins for coronary heart disease). In addition, there has been the recent introduction of so called 'lifestyle drugs' for the treatment of what have not previously been seen as medical conditions, such as obesity, baldness, impotence and mood disorders;

- **Increasing R&D expenditure** – The amount of money invested by leading companies in R&D has increased steadily, both in absolute real terms and also as a percentage of industry sales. The UK industry spent £3.5 billion on R&D in 2003, representing over 20% of total output. These increases are largely in response to the rising cost of drug development, decreasing R&D productivity and pressure from financial markets to create a stream of new blockbuster products;

- **Investment in biology** - Large firms have also been investing heavily to create in-house competencies in molecular biology, genetics and genomics. Many firms now

see themselves as integrated life science companies, which are increasingly dependent on biological knowledge for the discovery and development of new products;

- **The growth of the biotechnology industry** – in the last two decades thousands of small specialist biotechnology companies have been formed in North America and Europe. These are mainly biology based and the majority are focused on the development of human healthcare products. An increasing proportion of all new medicines are being development by these firms and the US Biotechnology Industry Organisation claims that some 30% of new drugs approved in the US now have their origin in the biotechnology sector (BIO, 2005);

- **R&D outsourcing** – Another response to the productivity crisis and the changing knowledge base of the industry has been a rapid increase in the formation of research collaborations and strategic alliances with small biotechnology and genomics firms. According to the Recombinant Capital database (www.recap.com) over 15,000 biotechnology related alliances were created between 1981-2003, with leading firms such as Glaxo SmithKline forming over 500 collaborations during this period. A number of the top 20 pharmaceutical firms now outsource 25-30% of their total R&D expenditure.

Despite these changes, the pharmaceutical industry remains one of the most profitable and rapidly growing sectors of the economy.

5.2   The changing pharmaceutical market place

Alongside changes in the structure of the pharmaceutical sector, the organisation of R&D and the product focus of the industry (i.e. the supply of drugs) there have been significant shifts in the pricing, distribution and marketing of prescription medicines. These have resulted in the creation of both new markets and new forms of demand. In large part these shifts have been driven by the activities of the industry and government, rather than in response to the changing needs of patients and professionals.

5.2.1   Regulation of the UK drugs market

The National Health Service (NHS) is a public service that receives the bulk of its funding from general taxation. As a consequence, it has always had to operate within a fixed budget not directly linked to user or patient demand. As well as the cost of staff, equipment, and buildings, expenditure on medicines is a major element of the healthcare budget, representing nearly 12% of total NHS expenditure. A number of specific mechanisms have been developed to control the drugs bill.

In the UK, where drug licensing is governed by the Medicines and Healthcare products Regulatory Agency (MHRA), there are three categories of drugs: prescription only medicines that require a prescription from a doctor, pharmacy drugs which can be sold without prescription, but only through a registered pharmacy outlet, and general sales list medicines which can be sold in supermarkets and pharmacy shops. The latter two categories are described as over-the-counter (OTC) medicines.

The sale of medicines to the NHS is highly regulated, with the majority of drug prices negotiated nationally. The pharmaceutical industry has been subject to profit regulation on brand name prescription medicines sold to the NHS since 1969. This regulation, known since

1978 as the Pharmaceutical Price Regulation Scheme (PPRS), involves a voluntary agreement between the Department of Health and the Association of the British Pharmaceutical Industry (ABPI). The PPRS aims to provide safe and effective medicines to the NHS at a reasonable price, whilst also promoting a strong and profitable pharmaceutical industry in the UK. The agreement involves regulating the profit that pharmaceutical companies can make on the sales of medicines to the NHS. It takes into account the level of expenditure on research and development and the costs of advertising, which can be can set against sales to the NHS, and also controls price rises. The Scheme covers around 80% of the medicines used by the NHS, which amounts to some £7 billion (Department of Health, 2003c). The PPRS agreement for 1999-2004 was intended to secure a 4.5% reduction in the price of medicines covered by the Act. As part of its remit to support a competitive pharmaceutical market in the UK, the PPRS allows pharmaceutical companies to set launch prices for new drugs. The US, Germany and Switzerland also permit this practice, but many other countries with a significant pharmaceutical market, including France and Japan, do not. Since 2003 the Department of Health (DH) has been in consultation on the next phase of the PPRS to succeed the 1999-2004 agreement, and has been discussing issues such as possible amendments to the scheme and the potential for deregulation.

Generic (non-brand-name) medicines sold to the NHS, community pharmacies and doctors who provide prescriptions to NHS patients are also subject to regulation. In 2002, 76% of NHS prescriptions were written generically and generic medicines accounted for 53% of prescription items dispensed in the community (Department of Health, 2003f). Introduced in 2000, the Maximum Price Scheme (MPS) for generic medicines sets a maximum tariff for common generics dispensed by prescription. The NHS reimburses pharmacies and other dispensers from its medicines budget for all drugs they provide as NHS prescriptions. Previously the NHS relied on competition in the market and incentives for community pharmacists to buy generics more cheaply than the headline price at which they were reimbursed, in order to deliver stable supply and value for money. However, price fluctuations in the generic drugs market in 1999 led to the introduction of the 2000 MPS legislation to ensure a reliable supply of generic drugs through pharmacies. In late 2003 the Department of Health launched a consultation on proposed measures to replace the Maximum Price Scheme in England, with a new voluntary agreement between the NHS, pharmacies and generic drug wholesalers and manufacturers. The new agreement, which would involve a new, recalculated drug reimbursement tariff, is intended to bring repayments to community pharmacies into closer alignment with cost prices of the medicines they purchase, whilst supporting a competitive market and retaining good value for the NHS. It would also exert some measure of control over pricing decisions on the sale of generics to NHS prescription providers. At present the new proposals still allow manufacturers to set prices on new products at their own discretion, with the proviso that they should be cheaper than an equivalent brand-name medicine.

Neither the PPRS nor the maximum Price Scheme (and its replacement) applies to over-the-counter (OTC) sales, medicines dispensed under private prescriptions and medicines that GPs are forbidden to prescribe on the NHS. OTC products are mainly distributed through community pharmacy practices based in chemists, high street retailers and supermarkets. Entry to the market has been regulated in order to ensure a viable pharmacy sector.

In the UK the NHS has been responsible, since 1987, for awarding contracts to local pharmacies entitling them to dispense NHS prescription medications. In 2001 the total market for prescription and over-the-counter medicines was £8.6 billion, of which the majority (£6.8 billion) was due to NHS prescription medicines (Office of Fair Trading, 2003). With such a

large proportion of revenue coming from NHS dispensing, it is extremely difficult for a pharmacy to survive commercially without an NHS contract. To open or relocate a pharmacy within a particular area the owners must apply to the local health authority (Primary Care Trust in England and Wales) for a license to dispense NHS prescriptions. In this way the number of pharmacies in each area is effectively controlled by the NHS. The process of applying for a licence is known as the 'control of entry' system – a set of criteria assessed by the Primary Care Trust or other relevant body to determine *"whether it is necessary or desirable for a new pharmacy to dispense"* (Department of Health, 2003 c).

In 2003 the Office of Fair Trading published a report detailing its investigation of the effect of control of entry regulations on the UK's community pharmacy sector (Office of Fair Trading, 2003). The report recommended that the control of entry process should be abandoned and an unrestricted market introduced. This would mean that a larger number of retail outlets would be able to sell OTC and general sales list products, in the interests of improving service provision and quality, as well as lowering prices through competition. In its response to this report the Department of Health (2003) did not support total deregulation, with the government wishing to maintain control of entry given the shortage of pharmacists and its desire to see the profession developing a 'new and stronger role' in the NHS. However, it has proposed to liberalise the entry requirements to promote greater competition, choice and access to OTC medicines and NHS prescribers. These include pharmacies that plan to open long for hours, consortia trying to establish 'one-stop' primary care centres and wholly mail order or internet-based pharmacies. It is hoped that this will help reduce the price of pharmaceutical products sold in the OTC market.

Mail order or internet pharmacies were previously required to operate from an existing pharmacy retail outlet, for which the control of entry application would be considered, but under the amended regulations this will no longer be necessary. The possibility of 'remote delivery' of pharmaceuticals offers potential both to increase the availability of NHS prescribing services to remote areas and less mobile individuals, and also the possibility of lower prices for OTC medicines by saving costs on establishing high street premises to work from. These pharmacy services will still have to apply to a local health authority for a dispensing contract and will be required to provide a full range of pharmacy services such as managing repeat prescriptions and promoting healthy lifestyles. Additional standards of professional practice, including data protection, patient confidentiality and safe delivery of medicines will be required of mail order and internet pharmacies. The Royal Pharmaceutical Society of Great Britain's Code of Ethics and Standards already includes professional standards for remote delivery of pharmaceuticals.

However, there is serious concern that the development of e-pharmacies will undermine the currently protected community pharmacy market, as drug manufacturers look to exploit the direct-to-patient channel. One scenario is that manufacturers will seek to vertically integrate/disintermediate the medicines supply chain and cream off much of the low risk chronic illness and repeat prescription business, leaving high street pharmacies with the less profitable and more difficult to treat cases. At the same time, high volume/low maintenance dispensing could go through new 'dispensing factories' centred on supermarket distribution networks, which would supply patients directly via mail order. Whilst this might be attractive to many consumers, it would fundamentally undermine the economics of the existing pharmacy sector at a time when the NHS wants the profession to be highly regulated and have a greater role. To a large extent the NHS has relied on the private sector subsidising the community pharmacy infrastructure, with the pharmacies generating enough profit to make it of interest for the retailer to support professional regulation. However, the increasing cost of

clinical governance and risk management, and the prospect of a major restructuring of the marketplace call this into question.

The liberalisation of the distribution of drugs through community pharmacies and the reform of the market for generic medicines may force changes in the PPRS and in 2003 the government published a discussion paper on the future of the scheme. However, it seems clear that despite a degree of deregulation, the market for prescription medicines in the UK will remain tightly regulated through central price controls for the foreseeable future.

5.2.2   The move towards over-the-counter drug sales

As part of the effort to control public health spending on medicines, successive governments have increased the number of previously prescription only drugs that are available to buy over-the-counter. The move to greater numbers of OTC drugs began in the 1980s through an initiative making it easier to reclassify prescription medicines to OTC status. Between 1983 and 1992 11 drugs moved from prescription to pharmacy status. After further streamlining of the process a further 40 drugs were reclassified between 1992 and 1996. In 2004 the UK became the first country to license statins for over-the-counter (pharmacy) use as a treatment for moderate risk of heart disease. The market for OTC medicines in the UK is approximately equal to one third of the NHS medicines bill.

When drugs are available without prescription members of the public are able to self-medicate and costs shift from public health to personal expenditure. Despite concerns over the safety, monitoring and efficacy of over-the-counter drugs, the move to OTC is likely to continue, as self-medication fits well with the current policy emphasis on increasing public participation and giving greater responsibility for healthcare to individuals. It also ties into the current plans to expand the role and responsibility of pharmacists in providing extended healthcare and health advice services to the public.

Although a move to over-the-counter sales may reduce the prescription only market for a particular product, it can be commercially attractive for older drugs about to lose patent protection, as it introduces them to a new (and often large) non-prescription market. Furthermore, drugs sold through pharmacies are not subjected to the profit regulations that affect prescription drug sales to the NHS.

In 2003, as part of the liberalisation of the OTC market the government announced that it was going to lift the ban on the advertising of OTC medicines for a wide range of conditions (MHRA, 2003). This allows pharmaceutical companies to use marketing and branding strategies to popularise OTC products that may also be available on prescription. At present, prescription medicines cannot be advertised directly to the public, although this has become a major area of policy discussion.

5.2.3   Direct to consumer advertising and 'disease mongering'

Direct-to-consumer advertising (DTCA) of prescription medicines through print and television advertisements has existed in the US since the early 1980s, but has only really developed since 1997 when the FDA relaxed its regulations on traditional media, and internet marketing. To date, such advertising is only permitted in the US and New Zealand, although there have recently been attempts to allow this throughout the European Union. The industry sees direct to consumer advertising as a means to raise awareness of particular products, expand markets and increase sales. Relevant companies argue that DTC marketing of

prescription medicines increases public awareness of some medical conditions that are under-diagnosed or under-treated, such as hypertension. By advertising, the companies claim they are providing health information on treatments that patients may not know about and are empowering people to make healthcare decisions based on greater knowledge. Since the late 1990s DTCA spending by pharmaceutical companies has grown from a relatively negligible level to some $3 billion/year (Medawar, 2001; National Human Genome Research Institute, 2004). There is evidence that DTCA is focused on creating and promoting blockbuster drugs, as the number of blockbusters and the US national drugs bill have both risen considerably since 1997. Indeed DTCA may now be necessary to create such high sales levels (Medawar, 2001).

Empirical research from the US has shown that DTC advertising is highly effective. Results of a survey carried out in 2000 found that two-thirds of Americans could recollect seeing a direct to consumer advert for a prescription medicine and 10% had asked their physician for the treatment (Woloshin, Schwartz, Tremmel and Welch, 2001). In response to the growth of DTC marketing, there have been concerns that such advertising favours the promotion of new drugs rather than established and proven therapies, that it often fails to clearly state the expected benefits of the medicine, and uses emotional appeals to persuade people to ask their doctor for particular treatments (Woloshin, Schwartz, Tremmel and Welch, 2001; Gollust, Wilfond and Hull, 2003). In addition, there are fears that this type of marketing encourages unnecessary use of prescription medicines, which will increase the cost of healthcare and expose people to unnecessary risks from the side-effects of therapy. In 2003 an FDA public meeting on DTC advertising (primarily of pharmaceuticals) found that, in general, such adverts increased awareness of products, but did not accurately convey risk information (National Human Genome Research Institute, 2004). At present, direct to consumer advertising of prescription medicines remains prohibited in the UK and Europe, although increasing use of the internet means patients and consumers have greater access to drug information websites, many of which are sponsored or run by pharmaceutical companies. The growth of DTCA will also enable the direct-to-consumer distribution of prescription medicines described in section 5.2.1 above.

More fundamentally, critics of DTC advertising also claim that it contributes to the medicalisation of normal human experience by persuading healthy people they are ill (Moynihan, Heath and Henry, 2002). In doing this, they accuse drug companies of 'disease mongering' – turning common experiences into something to be treated as a medical condition with drug therapy.

Apart from the promotion of new medicines, the internet is being increasingly used to promote genetic testing services offered by companies such DNA Direct and Genelex in the US and g-Nostics in the UK. A number of public interest and scientific organisations (Genewatch UK and the US National Human Genome Research Institute) have expressed concerns that direct-to-consumer sales of genetic tests removes the key role of healthcare professionals in advising patients. As a consequence, there is no guarantee that the consumer will get reliable information on the interpretation or the accuracy of the results, which often concern susceptibility to common complex conditions where no definite conclusions can be drawn from a result. There are also worries that such tests can have the effect of convincing healthy people they are at an elevated risk of illness and directing them towards unnecessary medication. Indeed, non-clinical tests are often advertised for lifestyle and nutritional analysis in combination with products or treatments produced by the same company. These tests often lack scientific validation and might be seen simply as a tool to increase product sales. A high profile and controversial example of web based consumer marketing is the use of a self-

administered patient questionnaire to assess an individual's risk of getting breast cancer, as part of the marketing of Myriad Genetics BRCA test for susceptibility to the disease. This has been criticised for causing anxiety amongst women identified by the questionnaire as at risk, only a few of whom would genuinely benefit from the test (Gollust, Wilfond and Hull, 2003). Furthermore, the lack of follow-up genetic counselling and interpretation of results presents a risk of misinterpretation, provoking unwarranted anxiety amongst test users (National Human Genome Research Institute, 2004). There are a number of other examples of internet based direct-to-consumer advertising of genetic testing services, some of which make false claims about the clinical utility of the test (Genewatch, 2002)

However, it should be stressed that the majority of internet sites providing genetic services are non-health related, offering mainly paternity testing or DNA banking (Gollust, Wilfond and Hull, 2003). In addition, many companies, which once promoted genetic tests through the internet, including the UK's Sciona, have withdrawn from the direct sales market after public criticism and now concentrate on promoting their services to health professionals (Genetics Interest Group, 2002). At present, there is little regulation of this type of marketing in the UK, and there have been calls to improve consumer protection and tighten the regulation of internet marketing of genetic testing services (Human Genetics Commission, 2003) The internet remains extremely difficult to police and the most realistic solution may be to regulate internet testing companies operating within national borders to ensure adequate counselling and interpretation of results, and hope that consumers prefer this safer option to more risky unregulated services. It should also be noted that so far there has been very little consumer demand for directly marketed genetic tests and it is unlikely that this situation will change in the near future.

5.3 The changing NHS

5.3.1 The modernisation of services and healthcare technology assessment

There has been a process of near constant change to the structure and organisation of the NHS over the last 20 years. The latest of these followed the election of the Labour government in 1997, which introduced Primary Care Trusts (PCTs) and more recently, Foundation Hospitals. The latest series of policy initiatives contained in the 2004 NHS Improvement Plan set out a vision of the health service in 2008 and places great emphasis on patient choice, the reduction of waiting lists, a streamlining of national targets, a more 'arms length' role for the Department of Health, a strengthened national inspectorate, the devolution of responsibility to local managers and staff, and an increased emphasis on the management of chronic diseases (Department of Health, 2004b). Many of these objectives have been a priority for some time and they continue the general trajectory of policy towards making the NHS more flexible and responsive to users.

Despite the many changes that have occurred in the formal organisation and management of the health service and the changes to the distribution and marketing of medicines described in the previous section, relatively few policies have had a major impact on the development and overall consumption of medicines in the UK. However, specific policies are encouraging greater use of particular drugs. For example, in March 2003 the Audit Commission highlighted the rapid rise in drug spending by PCTs, largely as a result of the implementation of national service frameworks (NSFs) and National Institute for Clinical Excellence recommendations (Audit Commission, 2003). Nearly half of the £540 million increase in spending on drugs by PCTs occurred in four areas (lipid regulation, anti-hypertensives, diabetes and psychoses) that had been prioritised by specific NSFs or in NICE guidance.

Healthcare technology assessment

The National Health Service Health Technology Assessment programme is a national initiative for ongoing evaluation of the effectiveness, appropriateness and cost of new medical technologies. The programme is funded by the NHS research and development section and managed from the National Coordinating Centre for Health Technology Assessment (NCCHTA) based at the University of Southampton. The NCCHTA is responsible for identifying and prioritising appropriate topics for health technology assessment. The Centre employs a broad definition of 'health technology' encompassing new drugs and equipment, but also procedures and all activities of healthcare professionals. The HTA programme is intended to be needs led and possible topics for HTA can be suggested through direct consultation exercises with NHS policy makers, managers and practitioners, as well as the Royal Colleges of Medicine, consumer and patient representative groups and specialist societies. The NCCHTA also receives input from the National Horizon Scanning Centre (NHSC) at the University of Birmingham and through direct submissions via its website. The role of the NHSC is to 'provide advance notice to the Department of Health in England and Wales of selected key new and emerging health technologies (including changing applications and uses of existing technologies) that might require urgent evaluation, consideration of clinical and cost impact or modification of clinical guidance' (NHSC website, 2005).

Within the NCCHTA suggested topics are prioritised by four advisory panels covering diagnostic technologies and screening, pharmaceuticals, therapeutic procedures, and disease prevention. Once priorities are agreed they are passed to the Health Technology Assessment Commissioning Board (HTACB), which is responsible for turning these inputs into viable research projects. Research is contracted out via invitations to submit proposals for primary research or the synthesis of existing evidence on selected health technologies. The calls are open to research institutions internationally and are subject to evaluation by the HTACB and the Health Technology Assessment Priority Strategy Group which ultimately decides which proposals to fund. The HTA program liaises with other funding bodies including the Medical Research Council and medical charities to ensure there is not an overlap in commissioned research. The findings on HTA programme research are then fed into the NHS commissioning process in order to facilitate the evidence-based adoption (or termination) of new or established technologies and practices.

The HTA program is also closely linked to the National Institute for Health and Clinical Excellence (NICE), which was established in 1999 to appraise new health technologies, including drugs, before they are introduced into the NHS. The Institute also covers medical devices, surgical procedures and other inventions for diagnosis and treatment. NICE has sometimes been described as the 'fourth hurdle'; before getting approval for NHS use, new drugs will not only have to prove that they are safe and effective, but that they are superior to existing products. NICE evaluations are based on clinical evidence, input from patients and companies, and measures of cost effectiveness. The NICE Appraisal Committee draws on a wide network of people including practitioners, patient and carer groups, academics, professional bodies, government and industry experts as well as technology assessment reports commissioned by the HTA programme. Recently it has given the general public a stronger say by creating a 'Citizens' Council' of lay people.

NICE does not investigate all new treatments, only those where there is uncertainty or doubt about the effectiveness of a drug and only at the request of the Department of Health. The Institute makes its decisions on a case-by-case basis and the three possible outcomes of evaluation are acceptance, either for general use or in particular specialities, approval for trial

use only, and rejection. This essentially constitutes a national rationing system based on expertise, which some feel conflicts with the development of innovation at local level and the autonomy of hospitals and doctors.

The very nature of NICE means that it is often surrounded by controversy. In July 2002, the House of Commons Health Committee called for NICE to be made fairer and more transparent. Others have been critical of its work, saying that it has yet to mature into the efficient prioritisation mechanism that is needed to ensure the best use of NHS resources (Maynard, Bloor and Freemantle, 2004). These critics believe that the role of NICE is too peripheral, because at present the NHS is able to adopt some expensive new technologies before they have been fully evaluated and that it should be involved in the withdrawal of technologies that are shown to be ineffective or inefficient.

To date NICE has achieved some success, although a number of decisions have been controversial and others have been modified after lobbying from patient/consumer groups or the pharmaceutical industry. One of the most contentious decisions made by NICE was in 2002 when it decided that the therapeutic protein beta interferon should not be made available to every patient with multiple sclerosis. After much debate the Government announced a risk-sharing scheme for MS drugs, in which payment to the companies supplying the drug would depend on the effectiveness of the therapy in practice. Another criticism of NICE came in August 2002 when it changed its decision on the drug Glivec. It had originally ruled that the drug should only be made available to a few patients suffering from certain forms of chromic myeloid leukaemia (CML), but after pressure from patients and doctors it amended this decision to include all cases of the disease. Recently the speed of NICE assessments has come under scrutiny over claims from cancer charities that it was delaying the availability of the drug Herceptin, which has been seen as a potentially life-saving therapy for women with early-stage breast cancer although it is not licensed for this indication and only a limited amount of clinical data is available. NICE has responded by placing Herceptin and a number of other cancer treatments on a special 'fast-track' evaluation service.

One of the main objectives behind the creation of NICE was a move to put an end to the 'post code lottery' in the prescription and availability of drugs. However, there is evidence that large variations still persist. A number of measures have been introduced to try to tackle this problem, including access to better information about the implementation of NICE guidance, the introduction of electronic hospital prescribing, improved data on NHS prescribing and further measures to disseminate best practice.

5.3.2 The development of genetics services

In June 2003 the UK Government published a white paper on genetics entitled *"Our inheritance, our future – realising the potential of genetics in the NHS"* (Department of Health, 2003a). The paper stated the Government's intention to maximise the use of genetics to improve healthcare and other services within the health service and to create a basis for utilising future developments in genetics in the NHS. It set out a series of policies under the following headings:

- Strengthening specialist genetic services
- Building genetics into mainstream services
- Spreading genetic knowledge across the NHS
- Generating new knowledge and applications
- Ensuring public confidence

In particular, the white paper envisaged a number of developments, which will influence the future of healthcare, including the individualisation of therapy, the personalisation of risk, an increase in the potential and use of genetic diagnostic testing, and the arrival of novel gene-based therapies, such as gene therapy. The Government also set out a series of steps, which it believed needed to be taken in order to modernise genetics services within the National Health Service and the wider field of UK genetics research. Proposals for specific action in the paper were intended to run until 2006 and are to be reviewed at the end of that time.

The established NHS genetics centres are specialist facilities, which bring together clinical geneticists, genetic councillors and genetics laboratories. Integrated centres of this sort will continue to be needed to meet the extra demands foreseen in genetic testing and could also be hubs for spreading expertise throughout the NHS. To this end, the paper proposed increased spending to upgrade facilities (£18 million over a three year period), increase the workforce, and train new councillors and laboratory staff.

The plans for spreading genetic practice throughout the NHS focused on supporting specific programmes, including piloting cancer service provision networks, screening and treatment services for selected conditions involving inherited genetic risk factors, and establishing a number of GP practices with a specialist interest in genetics. Spending plans also included £2 million for initiatives to spread genetic practice in hospital care and £2 million for primary care genetic initiatives. In terms of promoting genetic knowledge in the health service, the focus is on education. To this end the NHS Genetics Education and Development Centre was set up to address the needs of NHS staff at all levels, with its first priority to be general practitioners. The Centre has a number of objectives, including identifying the genetics knowledge, skills and attitudes useful for clinical roles; facilitating the integration of genetics into curricula and courses; identifying and developing resources appropriate to the needs of health professionals and supporting and disseminating learning from service development initiatives. It provides a web portal giving access to specialist genetic knowledge resources (see www.geneticseducation.nhs.uk). Other services such as NHS Direct are expected to keep up to date with genetic knowledge in the information they provide to the public.

The final strand of the plan involved providing increased support for healthcare related genetics research in the UK. The white paper detailed £4 million to be spent on pharmacogenetic research on existing drugs, £7 million on gene therapy research and an additional £2.5 million for gene therapy research specifically on cystic fibrosis, the UK's most prominent single-gene disorder. The plan also included support for other initiatives such as Biobank UK, pilots of near patient genetic testing and the work of the Genetics Knowledge Parks.

Although the white paper marked the most comprehensive and coherent policy for genetics in the NHS, the scale of new investment (~£50 million) needs to be set against the size of the overall NHS budget, which was £64 billion in 2004. In other words, the amount of new funding is very small and is unlikely to have a significant impact either on service development or delivery outside existing regional centres and laboratories.

Genetic Knowledge Parks

Following recommendations made in the NHS plan, a Genetics Knowledge Challenge Fund of £15 million was set up in a joint venture between the Department of Health, the Welsh Assembly and the Department of Trade and Industry. This money was used to set up six Genetics Knowledge Parks in England and Wales. The six parks, based in London, Oxford, Newcastle, the NorthWest, Cambridge and Cardiff, are conceived as multidisciplinary centres

combining access to academic and clinical research with industrial and public health interests. The remit of the Parks is to work with public and private funders to:

- Support and carry out clinical research in genetics related to healthcare;
- Make sure the NHS is best placed to take advantage of advances in genetics;
- Enable UK companies to exploit the latest developments.

The Genetics Knowledge Parks will also have a role in promoting public understanding of genetics and analysing the ethical, legal and social issues associated with genetic technology and practices.

The Parks are designed to act as parts of an overlapping network, each with a specialist focus of their own. For example, the London and Oxford Parks are identifying genes involved in coronary heart disease and developing diagnostics. The Knowledge Parks also have several common objectives; to investigate ways of developing genetic services in primary, secondary and tertiary levels of healthcare, to provide education and training, and to promote public understanding of genetics. Most of the Parks will be involved with taught postgraduate courses for healthcare professionals, including genetics specialists and staff from a non-genetics background. As well as science-based courses, programmes will include law and bioethics, genetic counselling and science communication. Other training and education programmes will be provided to non-healthcare personnel and the public. Finally, the Knowledge Parks will also provide a hub for expert policy advice on genetics for NHS managers and the government.

5.4   Changing professional practice

5.4.1   Professions in the changing NHS

The network model for the organisation of the NHS favoured by the current government, and the policy changes that are guided by it, have had a considerable impact on the mode and nature of professional practice within the health service. Part of the old hierarchical structure of the NHS included strict demarcation between clinical professions. The network model envisions greater flexibility, interaction and even interdisciplinary methods of working. This includes expanding and changing the duties of certain groups, such as nurses, therapists and pharmacists. The NHS Modernisation Agency is driving through a programme of reform, based on a national set of protocols for dealing with common conditions and determining which staff are best equipped to deal with them. Training and career development pathways are being established to enable appropriately qualified staff to expand their roles, with extra funding directed towards this goal. Nurses are to be given limited prescribing powers as well as powers to treat accident and emergency patients with minor ailments, order diagnostic tests and make referrals. Midwives may lead responsive childbirth services and primary care groups are intended to bring together multiple forms of expertise in one location. In the community, primary care centres are designed to be 'one stop shops' for primary healthcare where general practitioners, opticians, dentists, pharmacists and social care workers are all grouped together under one roof. The idea is that multidisciplinary interaction and co-ordination between these different healthcare professions will provide an improved standard of care for patients.

5.4.2   A new role for pharmacy

The changing face of healthcare also includes changes for pharmacists. With focus on the greater utilisation of their skills, the role of pharmacists is moving away from remuneration for dispensing medicines towards being rewarded for providing an extended range of services. In 2003 the Government published 'A Vision for Pharmacy' in which it reaffirmed its commitment to strengthening the role of the profession, whilst at the same time seeking to create a financial and contractual framework that would enable both greater working flexibility and a more responsible professional role (Department of Health, 2003d)

The Chief Pharmaceutical Officer has produced a list of the 10 key roles for pharmacists which are intended to form the basis of local care provision and which emphasise the direction of pharmacy in the future (Department of Health, 2003d, p7). Community pharmacies are considered the first point of contact in primary care for many people. This role is partially fulfilled through the location of pharmacies in primary groups and centres to serve as part of a multidisciplinary primary care environment. Pharmacists, in many primary care centres, have already been working alongside GPs as prescribing advisors. Pharmacies will also form part of the NHS network through the NHS Direct internet, digital and telephone services, which will often refer patients to their local pharmacist. Some pharmacies will contain NHS Direct information points where customers and patients can access health and health service information. Furthermore, it is planned that pharmacies will be involved in providing medicines and information to deprived areas where no other healthcare services exist.

In line with the changing function of pharmacies as sources (or resources) of health information, the expanded role of pharmacists includes that of providing medical and pharmaceuticals advice. The increasing range of over-the-counter drugs is intended to provide practitioners with a greater range of medicines at their disposal, and will allow them to encourage self-medication for patients with minor ailments. Medicines management programmes are being developed to enable pharmacists to work on a one-to-one basis to advise patients, especially those with chronic conditions, on the best use of their medication in order to reduce the incorrect use and waste of drugs. Greater emphasis on repeat prescriptions will allow pharmacists to provide a regular managed supply of medication to chronic condition patients without necessitating one-off prescriptions from a GP. Increased supplementary prescribing will also allow pharmacists to assume the management of continuing care after patients have been assessed by an independent prescriber, including regulating dosage and prescribing a range of other drugs or specialist products. In many ways the objectives of medicines management are similar to managed care – to reduce the burden on GPs, to reduce the level of hospital admissions and facilitate increased patient responsibility for individual healthcare. Following the nurse prescribing program some pharmacists will be able to assume expanded prescribing duties as well.

Funding and training opportunities are part of supporting these changes, but they will also be addressed through new pharmaceutical service contracts and by relaxing the strict regulations on interaction between various NHS departments and local pharmacies, an increasing number of which are part of commercial chains. Hospital pharmacy services are also changing. Hospital based pharmacists extended duties include working on admission wards, determining the correct medicines for patients as early as possible in their stay, working with nurses in supervising in-hospital medicine self-administration programmes and participating in the medicines management programme for hospitals.

5.4.3   The move to evidence-based medicine

Evidence-based medicine (EBM) is a general method of informing clinical decision making about the care and treatment of individual patients. Initially developed in Canada in the 1980s, it has since spread to many health services in different countries, including the NHS. The UK has established centres for evidence-based practice in adult medicine, child health, surgery, general practice, nursing, pharmacotherapy and other disciplines. There are also centres for teaching and the promotion of EBM and the review and dissemination of current clinical information, such as those found at Oxford and York. Despite its spread, evidence-based medicine remains a topic of debate, attracting criticism as well as endorsement within the medical community, patients and the lay press.

The process of evidence-based medicine involves addressing a clinical problem as a series of empirical questions, systematically locating and critically appraising data from contemporary research relevant to the issue and then using this evidence as a basis for practice. Evidence is gathered from the medical research literature, including the results of clinical trials, and can be applied to any aspect of clinical diagnosis, prognosis or management. Part of the aim of EBM is to bridge the gap between clinical research and clinical practice, and improve the quality and efficacy of the patient care provided. It is in effect a clinical learning strategy that helps keep doctors and clinicians from relying solely on increasingly out of date primary training and also serves as a way of filtering useful knowledge from a surfeit of new data.

There have been criticisms that evidence-based medicine is a charter for cost cutting on the NHS, or that it is a form of 'medicine by recipe'. However, the theory of EBM is to utilise the most efficient and effective treatment to improve quality of care. This treatment may not be the least expensive option, and all external evidence is intended to be interpreted in the light of individual clinical experience, not replace it.

Evidence-based medicine has applications beyond the immediate remit of clinical staff. It has been used by healthcare purchasers with little knowledge of medicine to inform their purchasing decisions and has also been adopted by some patient/consumer groups as a means of promoting patient choice by finding out about the various options in areas such as pregnancy and childbirth.

5.5   Changes to the regulation of new medical technologies

The way in which genetic research and the development of healthcare products is regulated can have a major impact on the process of medical innovation. It is essential that public confidence is maintained in both the conduct of research and the safety of new medicines. In general, in the UK basic and early stage clinical research is regulated through the governance mechanisms of the scientific and medical professions, as well as the government's non-statutory advisory system. In contrast, the development, approval and marketing of new drugs and medical devices is strictly controlled through European and national regulatory agencies.

The oversight of human genetics research

The Human Genetics Commission (HGC) is the advisory body charged with analysing current and potential developments in human genetics and advising ministers. The committee was set up in 1999 as part of measures to update and streamline the existing governmental advisory system on biotechnology in the wake of the GM food crisis. The HGC is a non-statutory body and as such has no direct regulatory function. Instead its remit is to advise ministers on

developments in genetic technology that will affect matters of public policy, the likely impact of new genetic procedures and uptake of new genetic-based technologies in the NHS. It is also responsible for relaying to ministers the concerns of the public and other stakeholders. To fulfil its monitoring and assessment remit the HGC has a number of subgroups and working parties devoted to specific issues, including genetic testing and the production of databases of genetic information. It also works closely with other advisory bodies, such as the Gene Therapy Advisory Committee, on relevant issues. Recent work has included consideration, in conjunction with the Human Fertilisation and Embryology Authority, of stem cell research and therapy. To gather information the HGC commissions research, utilises consultation exercises with relevant stakeholders, organises open meetings, and has a consultative panel of individuals affected by a genetic disorder. Each specific topic addressed is usually presented in the form of a report to the relevant government department or minister.

The HGC has played an important role in helping anticipate and consider some of the key issues raised by contemporary developments in genetics and the biosciences. It forms a key part of a well-developed system of scientific expert advice to government that has been largely successful in ensuring broad support for research on genetics and biotechnology. There is little evidence to suggest at present that public confidence and trust in this area of science is being significantly eroded, although this should not be taken for granted.

The regulation of medicines and medical devices in Europe

Within the European Union member states generally have their own national regulatory body for assessing new medicines, but all of these are now subordinate to the centralised directives on medicines assessment that act through the European Medicines Agency (EMEA) and the European Commission itself.

The European Community has a longstanding interest in this area, with its first directive on pharmaceuticals regulation issued in 1965 in response to the incidence of severe side effects caused by the administration of thalidomide to pregnant women. The UK did not join the EC until 1973, around which time two further initiatives were being introduced which laid the groundwork for a single centralised European pharmaceuticals market and formed the basis of the current legislative system. This multi-state procedure allowed member states to take into account existing market approval for medicinal products in another member state. It was designed to reduce the duplication of assessments for individual products by each country and introduce a faster, more efficient authorisation process. It was also hoped this would encourage more universal and harmonised levels of approval across Europe. To facilitate this process the Committee for Proprietary Medicinal Products (CPMP) was set up. The second procedure known as concertation was established specifically to deal with the assessment of biotechnology derived medicinal products, which required a high level of specialised knowledge. Under this agreement, each member state was required to consult with the others before making a final decision on whether to grant, refuse or withdraw marketing approval for a biotech-based product.

The current licensing system builds on both of these procedures and adopts a more robust approach to resolve previous difficulties caused by inter-member state disagreements. EMEA was set up in 1995 with its headquarters in London. It is a decentralised agency of the European Commission and incorporates the CPMP (now called the Committee for Medicinal Products for Human Use (CHMP) among its departments. The EMEA and the satellite national medical product evaluation agencies act in a similar capacity to the US Food and Drug Administration Agency (FDA). Together they are responsible for evaluating the safety,

quality and efficacy of medicines for both human and animal health. The agency is ultimately answerable to the EC, which issues the final decision on market approval for specific products. These decisions are now binding on all member states. Other responsibilities of the EMEA include the designation of orphan drugs, pharmacovigilance and post-market monitoring of approved drugs, and providing scientific advice on relevant matters to the EC. An orphan drug, in the EU designation, is one that is intended for the diagnosis, prevention or treatment of a serious (life-threatening) or chronic and debilitating condition that affects five or fewer people per 10,000 of the EC population. More frequently occurring diseases can also be considered if they are serious and chronic at the same time and the profit made from marketing such a drug would not be expected to justify its development (European Parliament, 2000). An orphan product must also show significant clinical benefit to those affected, and treat an unmet need (i.e. where there is no satisfactory existing therapy). As an incentive to pharmaceutical manufacturers, products that achieve orphan drug designation are granted a 6-10 period of market exclusivity and exemptions from market-approval fees (Louet, 2000). Individual member states can also offer tax credits for clinical studies on orphan products or on corporate taxes. The EU recently clarified that orphan drug legislation also applies to tropical diseases if they have a low prevalence in the Community (Gericke, Riesberg and Busse, 2005).

The world's two largest pharmaceutical markets, Europe and the US, are often compared in terms of the speed and efficiency of their respective regulatory agencies (EMEA and the FDA). The DTI sponsored Biotechnology Innovation and Growth Team (BIGT) report published in 2003 raised concerns that the EMEA evaluation process is too slow compared to the US and could put the UK bioscience industry at a competitive disadvantage (BIGT, 2003). However, a study produced by the Tufts Center for the Study of Drug Development in 2000 (Tufts CSDD, 2000), which compared the regulation of biotech drugs approved in both the US and EU between 1995 and 1999, found that the EU procedure was quicker at granting marketing approval than the FDA. The difference in times was greatest when considering new recombinant DNA products, although the FDA was faster at approving monoclonal antibodies and antisense drugs. A 2002 study published in the European Journal of Cancer Research (Anon., 2002) highlighted longer waiting times for marketing approval for anti-cancer drugs and anti-HIV drugs between 1995 and 2001 through the decentralised EU procedure compared with the US FDA. Explanations for this included the 11 languages that all European drug approval reports must be presented in and the potential for disagreements between member states resulting in decisions being passed to the CPMP for potentially lengthy arbitration. Another 2002 report, by CMR International, shows that between 1992 and 1996 Europe was the first choice of market for the primary launch of new medicines by the world's top 10 pharmaceutical companies, but in the period 1997-2001 this trend was reversed and the US became the first choice market for first time pharmaceutical launches (CMR International, 2002). Median approval times for the EC centralised procedure have been somewhat longer when compared to the FDA over the period 1997-2001, but the CMR report believes the switch in the favoured choice of market was more due to significant improvements made in FDA approval times in the late 90's (following the FDA Modernisation Act of 1997 and the introduction of new fast-track procedures) than failures in the EMEA application process. None the less, the authors of the BIGT report are keen to stress that it is in Britain's interest to promote further streamlining of the EU process in order to compete with the US.

In 2002 the UK Medical Devices regulations came into force, consolidating all previous regulations on medical devices into a single piece of legislation. This also brought into effect in UK law, the EC In Vitro Diagnostic Medical Devices Directive ((98/79 EC). The IVDD

Directive is intended to help create a single market across EC member states for in vitro diagnostic (IVD) products and to reduce technical barriers to trade. The Directive is designed to apply common regulatory requirements for IVD's across Europe where the level of regulatory control is proportionate to the degree of perceived risk for device users if the product fails to perform as intended. The highest risk category will include some tests for HIV, Hepatitis and some products used to test donated blood. The manufacturers of these high-risk products will be required to have their systems inspected and verified by a Notified Body for each member state – in the UK the designated body is the MHRA. Other than the test for phenylketonuria (PKU), all genetic tests are currently deemed low-risk and are subject to self-certification only (Hogarth *et al*, 2005). In general the Directive aims to set minimum standards for the safety, quality and analytical validity of tests, and in doing so imposes certain quality assurance and quality control requirements on testing laboratories and the need for CE marking on some 'in house' diagnostic tests. This has had an adverse effect on a number of NHS genetics and virology units, with several commercially available assays being withdrawn.

The regulation of medicines and medical devices in the UK

The current UK framework for regulating medicines acts through a process of licensing of pharmaceuticals. The legislative basis for this resides in European legislation and also in the UK Medicines Act 1968. The body responsible for overseeing this process in the UK is the Medicines and Healthcare products Regulatory Agency (MHRA). It was formed in April 2003 and replaces both the Medicines Control Agency and the Medical Devices Agency, combining both their functions to create a single organisation responsible for evaluating both new medicines and medical devices. The MHRA is an executive agency of the Department of Health and is accountable to UK ministers in the Departments of Health and Agriculture.

The activities of the MHRA include providing UK marketing licences for approved drugs and medical devices, monitoring and regulating all clinical trials of medicines carried out within the UK, reporting adverse incidents with medical devices, carrying out post-marketing surveillance of approved drugs, producing defective medicine assessments, issuing safety alerts and communicating its findings on safety and efficacy. The MHRA also has responsibilities to act as a national regulatory agency within the European Community network, carrying out work delegated by the EMEA and enacting medicines marketing approval or refusal decisions made by the EC within the UK framework. In 2002/3 the MHRA was the third most popular choice (after France and Sweden) of 'rapporteur' under the centralised procedure for biotechnological and specialised pharmaceuticals, but was not used as a reference member state under the multi-state recognition process for other drugs. There is no evidence to suggest that the Agency presents a significant barrier to the approval of new medicinal products over and above those already imposed by the centralised European procedure.

As already highlighted in previous chapters, there are a number of areas where the regulatory framework for genetic and biological technologies is still being created. In particular, the process of validating new genetic tests for common conditions and the requirements to demonstrate clinical validity and utility with respect to pharmacogenetic tests is still under discussion. The specific regulations relating to cell processing for some stem cell and *ex vivo* gene therapies have also to be finalised.

5.6   Supporting the development of innovative health technologies

The promotion of science, technology and innovation has become a major priority for government in recent years. To this end, the NHS Plan (2000) committed the government to changing the relationship between the NHS and the private sector, and in particular, the relationship to the pharmaceutical and biotechnology industry. It set out an initial set of policies to streamline the work of research ethics committees to ensure faster and more efficient recruitment of patients into clinical trials, as well as developing a strong set of national research and development programmes. These were elaborated and supplemented in the Department of Health Science and Innovation Strategy (2001) which established a series of major science and innovation priorities, including:

- To develop a major research and development programme in genetics and health;
- To implement measures to improve the competitiveness of the pharmaceutical and other healthcare industries;
- To develop and implement a new strategy for technology development and transfer;
- To develop a more strategic approach to promoting innovation in the NHS;
- To harness new information and communication technologies to promote health;
- To strengthen partnerships between the NHS, industry, the universities, Research Councils and other funders to promote synergy in the science base;
- To improve the research infrastructure in the NHS;
- To introduce new arrangements to support science in the NHS.

The commitment to genetics R&D was taken forward in the White Paper and through the creation of the Knowledge Parks described above. The Department also established the Pharmaceutical Industry Competitive Task Force (PICTF) in 2000 to look at the action needed to ensure the UK remains an attractive place for the pharmaceutical industry to locate its R&D facilities. In 2003 a similar Task Force was established for the Healthcare Industries. The PICTF report published in 2001 (PICTF, 2001) recommended a number of measures to meet this objective, including: streamlining licensing procedures for research involving animals, improving the use of NHS databases for research, co-ordinating government and industry activities on a number of European policies, and improving the efficiency of the organisation of clinical trials.

In the last few years several other initiatives have been undertaken to provide greater support for clinical research and development. In November 2003 the Department of Trade and Industry (DTI) sponsored Bioscience Innovation and Growth Team (BIGT) published a report Biosciences 2015: Improving National Health, Increasing National Wealth, which aimed to improve the performance of the UK biotechnology sector by identifying any barriers that could significantly hold back the growth of bioscience in the UK (BIGT, 2003). In particular it recommended a series of policies, including the creation of a National Clinical Trials Agency to support excellence in clinical trials and clinical research in the NHS, improving the regulatory support for new product development, improving the financing of biotechnology firms, creating a network of bioprocessing centres, and measures to promote interdisciplinary education.

The Research for Patient Benefit Working Party (RPBWP) was set up to bring forward practical proposals to implement the recommendations made in the BIGT report and a similar inquiry by the Academy of Medical Sciences. In June 2004 the Government announced a number of measures to improve the performance of the NHS in the development of new medicines. In conjunction with the Working Party recommendations, a UK Clinical Research

Collaboration (UKCRC) has been established to speed up the development process, with £24 million dedicated to Alzheimer's stroke, diabetes, mental illness and children's medicines. The Collaboration will bring together NHS professionals, PCTs and special health authorities, and the charitable sector to co-ordinate the use of existing funds and to develop incentives for NHS clinicians to become active in research. Following suggestions in the RPBWP report, the Clinical Research Collaboration will co-ordinate moves to build up the NHS infrastructure to support clinical research. These include a strategic analysis of current clinical research activity, establishing a UK Clinical Research Network and promoting the development of the UK's research workforce through a UKCRC subgroup on academic medical careers. The UKCRC is also committed to expanding the national capacity for research in experimental medicine. In 2004 the Government published a ten-year investment framework for science and innovation alongside its annual spending review. The framework set out the intention to capitalise on the increased investment in the NHS, with the Department of Health planning to increase the NHS R&D budget by £25 million per annum over a four-year period.

Many of these policies have been consolidated in a new national health research strategy for the NHS, which was launched in January 2006 (Department of Health, 2006). This has the aim of:

- Establishing the NHS as an internationally recognised centre of research excellence;
- Attracting, developing and retaining the best research professionals to conduct people-based research;
- Commissioning research focused on improving health and care;
- Strengthening and streamlining systems for research management and governance.

The strategy places particular emphasis on increasing public research funding, supporting clinical research in partnership with industry and creating an environment that will foster clinical and translational research. In particular, it proposes to establish a National Institute for Health Research in England as a virtual body, create a clinical research network covering the population of England to support high-quality research for all diseases and areas of patient need, expand the NHS investment in clinical research facilities for experimental medicine, and provide the NHS support for key technology platforms so that leading-edge research can thrive (Ibid.). In turn these initiatives were supported by policies aimed at developing research staff careers, providing new mechanisms for funding, supporting and managing NHS research, improving the research infrastructure (e.g. implementation of the electronic patient record), and fostering adoption of evidence based best practice.

Chapter 6.   Summary and conclusions

The previous sections have briefly described the current state of development of the most important genetic and biological therapies and diagnostics, as well as recent changes affecting the development and use of medicinal products. This chapter aims to summarise these findings and draw out the main conclusions for both policy and practice.

6.1   Assessing the current and future development of genetic and biological technologies

As mentioned in the introduction, trying to assess the future development of new technologies is a demanding and problematic endeavour. This is due to the wide range of factors that determine success and the high levels of technical, commercial, clinical and regulatory uncertainty that often mark early medical innovation. Because of this, previous work on technological forecasting has established that it is very difficult to assess accurately the prospects for an emerging technology much more than three years into the future. The best that can realistically be achieved is a crude assessment of which technologies are currently being successfully developed and used in the clinic, which ones may be adopted in the medium term (3-5 years) and which ones are unlikely to enter widespread usage in the next five years.

Criteria for successfully developing new medical technology

Historically, much of the emphasis of economic and technology assessment in the area of biomedicine has focused on products that are reasonably well established and are on the market or close to market launch. However, there are a number of reasons why a broader analysis of the factors shaping the dynamics of development and adoption may need to be used in the case of the genetic and biological technologies featured in this report. Firstly, many of the innovations described earlier are novel and few have clinical or commercial precedents that can be used to guide either their exploitation by industry or their use in practice. Secondly, a number of them raise important social, ethical and legal issues (ELSIs) and are surrounded by a degree of uncertainty over how they will be controlled by regulatory authorities.

To help guide the analysis of early innovation and take into account these other factors, a conceptual framework derived from work in the sociology of technology has been used. In particular this draws on the idea that in order to be successful, emerging technologies must meet a series of important criteria by achieving most, if not all, of the following:

- Scientific proof of principle;
- Demonstration of safety and therapeutic efficacy;
- Successful adoption (integration into clinical practice);
- Establishment of a viable business model for their commercial exploitation;
- Resolution of any important social and ethical issues;
- Creation of a stable regulatory framework;
- Enrolment of public support and legitimation.

This list is based on empirical studies, which have shown that successful market launch, adoption and diffusion is a complex technical, clinical, social and political process. For example, a new technology may work well in experimental settings, but if it involves the use

of a large and complex infrastructure (e.g. cell processing) this may severely limit its adoption into routine healthcare. Furthermore, if new technologies, such as stem cells, are surrounded by ethical controversy this may also severely impact on their usage even if they can be shown to be effective.

The idea that early biomedical innovation involves a complex series of steps is captured in the idea of 'entrenchment':

> *'... the notion of entrenchment ... conceptualizes the processes in which new technological options, through the interactions between a variety of actors, become viable and established practices in society, both satisfying and modifying needs and interests.'* (Koch and Stemerding, 1994)

To become entrenched into routine healthcare a new medical technology must be safe and effective, but must also be available as a commercial product, fit into established working practices, command the confidence of patients and be regulated in an enabling manner. Once products become well established in mature markets and widely used clinical procedures, it is often forgotten that they were surrounded by uncertainty in the past. Organ transplantation is a good example of a technology that is now routine and uncontroversial, but when first developed (in the 1960s) was seen as radical and surrounded by both medical and ethical debate. As part of the successful adoption of organ transplantation, new medical procedures and health service facilities were created, new businesses were developed to support transplant technology, new clinical governance frameworks were put in place and new social norms established to enable donation. In other cases, scientifically attractive options for new technologies failed due to lack of clinical or commercial support (Blume, 1991).

The entrenchment of new genetic and biological technologies

Using this framework it is possible to analyse the extent to which the technologies described in this report have become, or are in the process of becoming, entrenched in different ways. Table 6.1 summarises the current state of development of the main genetic and biological technologies described in Chapters 2-4. These data provide a measure of the length of development since proof of principle (date of the first product on the market), breadth of application (the total number of products on the market at the end of 2004), the extent of market creation, diffusion and integration into clinical practice (as measured by global sales or number of patients treated in the UK), the number of products that may reach the market in the next 3-5 years (as indicated by the number of products in late stage development[2]) and the broad level of industrial interest.

Table 6.2 summarises data on the main scientific/technical, commercial, clinical, ethical and regulatory barriers facing each technology. This is intended to provide a rough qualitative measure of the extent to which a given technology has become entrenched in a particular domain.

Drawing on data from both tables it is possible to divide genetic and biological technologies into three broad groups as follows.

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[2] This indicator has been chosen as the best measure of new products likely to reach the market as 50-70% of new drugs in Phase III receive marketing approval. The average length of Phase III is ~3 years (plus another 1-2 years to get marketing approval). It is therefore unlikely that any product not already in Phase III by the end of 2004 would reach the market before 2008.

1. **Technologies that are well entrenched in the clinic** (i.e. face few major social or economic barriers to their further development, have a reasonable number of products in late stage development and significant commercial interest). These include:

    -   *Genetic testing for monogenic disorders* – these were first developed in the 1970s and are now widely used with over 100,000 molecular genetic tests carried out each year in the UK. A small, but steady stream of new tests is entering the market. The main barrier to further expansion is the finite number of new monogenic diseases that exist, the very small market for each test and the subsequent lack of commercial interest. As a result, innovation will continue to be driven by the public sector;

    -   *Therapeutic proteins* – these were first developed in the early 1980s and more than 50 protein drugs are now on the market with global sales of over $37 billion. A steady stream of new products is entering the market. The main barrier to further expansion is the difficulty of demonstrating safety/efficacy;

    -   *Monoclonal antibodies* – these were first developed in the 1980s and some 25 products are now on the market, with global sales of over $4.5 billion. A relatively large number of new products are likely to enter the market in the next few years. There are no major barriers facing their further development at present beyond the usual requirements to demonstrate efficacy and safety.

    The medium term prospect for an expansion of these technologies is therefore very promising and they raise few new social, ethical or practice issues.

2. **Technologies that are starting to become entrenched in the clinic** (i.e. have a level of commercial interest, but sill face a number of significant social and organisational barriers and only have a small numbers of products in late stage development).

    -   *Pharmacogenomic drugs* – the first product of this sort (Glivec) was approved in 2001 and now has sales of over $1 billion. A small number of new products are likely to enter the market in the next few years. The main barriers to further expansion are difficulties in demonstrating safety/efficacy and a possible lack of commercial interest in small or potentially segmented markets.

    -   *Pharmacogenetic drugs/tests* – the first molecular genetic PGx test was available in the early 1990s. A small number of new products are likely to enter the market in the next few years. They face a number of barriers to further expansion, including, the difficulty of validating good gene/drug response associations, a lack of commercial interest in segmented markets, the need to establish a genetic testing service infrastructure, unresolved ethical questions about the use of genetic data and some regulatory uncertainty.

Table 6.1 Summary of current state of development of different genetic and biological technologies

Technology	First product in routine clinical use/ on the market	Total number of products in use/ on market	Total sales/ number of patients treated	Level of industrial interest	No. of different products in late stage development (Phase III or equivalent)
Genetic testing - monogenic conditions	First biochemical tests for sickle cell in 1970s.	>300 (UK)	~100,000 molecular genetic tests a year in UK	Low/ moderate	Unknown
Therapeutic proteins	Humulin (1982) - recombinant insulin.	>50	$37 billion worldwide (2005)	Moderate	5-10
Monoclonal antibodies	Orthoclone (1986) - organ transplant rejection.	25	$11 billion worldwide (2003)	High	25
Pharmacogenomic drugs	Imatinib (Glivec) (2001)	<5	~ $1.5 billion worldwide (2004)	Moderate	<5
Pharmacogenetic tests	TPMT (1991)	<5	<5,000 biochemical tests a year in UK	Moderate	5-10
Genetic testing - common conditions	APOE4 test for Alzheimer's (1995).	<5	<5,000 tests a year in UK	Low/ moderate	<5
Stem cells – adult	Peripheral blood HSC transplantation for cancer (1990).	1 (but several variant HSC therapies)	Over 2,000 patients treated in UK in 2002	Moderate	<5
Gene therapy	Gendicine (2003) - P53 cancer therapy (Chine only).	1 (China only)	-	Low	<5
Cancer vaccines	Melacine (2001) - vaccine for melanoma (Canada only).	0 (first product withdrawn)	-	Moderate	<10
Stem cells - embryonic	None	0	-	Low	0

Table 6.2 Summary of the main barriers facing the future development of different genetic and biological technologies

Technology	Scientific/ technical barriers	Commercial barriers	Clinical/ practice barriers	Social/ ethical issues	Regulatory concerns
Genetic testing - monogenic conditions	No major problems, but limited number of single gene disorders.	Small markets for tests	-	Ethics of genetic testing	Need to link to genetic counselling
Therapeutic proteins	Difficulty of showing safety/ efficacy in new products	-	-	-	Regulatory framework for biogenerics
Monoclonal antibodies	No major problems, but scale production is difficult.	-	-	-	-
Pharmacogenomic drugs	Difficulty of showing safety/ efficacy in new products.	Segmented markets	-	-	-
Pharmacogenetic drugs/tests	Validation of gene/ drug associations.	Segmented markets	Need for genetic testing infrastructure	Ethics of genetic testing	Regulatory framework for PGx not finalised
Genetic testing - common conditions	Validation of gene/ disease associations.	-	Need for genetic testing infrastructure	Ethics of genetic testing	Issue of clinical validity/ utility unresolved
Stem cells – adult	Most clinical research still at early stage.	No viable business model established	Need for cell processing infrastructure	-	Regulatory framework not finalised
Gene therapy	Difficulty of showing safety/ efficacy in new products.	-	-	Major safety concerns	Regulatory framework not finalised
Cancer vaccines	Difficulty of showing safety/ efficacy in new products.	No viable business model established	Need for cell processing infrastructure	-	Regulatory framework not finalised
Stem cells - embryonic	Research still at very early stage.	No viable business model established	Need for cell processing infrastructure	Use of embryonic material	No regulatory framework

- *Genetic tests for common conditions* – the first genetic test for APOE4 (Alzheimer's) was introduced in 1995. Only a small number of diagnostics for common conditions are likely to reach the market in the next few years. They face a number of barriers to further expansion, including, the difficulty of validating strong gene/disease associations, the need to establish a genetic testing service infrastructure, unresolved ethical questions about the use of genetic data and some regulatory uncertainty.

- *Adult stem cell therapies* – the first peripheral blood HSC transplant for the treatment of cancer took place in the early 1990s. Only a small number of new stem cell therapies are likely to reach the market in the next few years and these will mainly be variants of established HSC therapy. Stem cell therapies face a number of barriers to further expansion, including the fact that most clinical research is still at an early stage, no viable business model for their commercial exploitation has been established, the need to create a cell processing service infrastructure, and some regulatory uncertainty.

An expansion of these technologies in the medium term is therefore likely. However, whilst individual products are now widely used, as a broad technology each of them has yet to be fully entrenched in a mature market or established set of clinical practices. Each technology has demonstrated proof of principle, but still faces significant technical difficulties. With the exception of pharmacogenomic drugs, such as Glivec, they will also have to overcome a number of commercial, clinical, ethical and regulatory difficulties before they can be fully entrenched.

3. **Technologies that have yet to successfully enter the clinic** (i.e. have relatively little commercial interests, still face a number of significant social and economic barriers, and only have small numbers of products in late stage development).

- *Gene therapy* – the first gene therapy product gained marketing approval in 2003, but is only licensed in China. No other therapies are close to market. They face a number of major barriers to further development including, difficulty in showing safety/efficacy of products, general safety concerns about the use of viral vectors and some regulatory uncertainty.

- *Cancer vaccines* – the first cancer vaccine was licensed in Canada in 2001, but was subsequently withdrawn. A small number of products may reach the market in the next few years. They face a number of major barriers to further development, including difficulty in showing safety/efficacy of products, the lack of a viable business model for personalised vaccines, the need to create a cell processing service infrastructure and some regulatory uncertainty.

- *Embryonic stem cell therapies* – no therapy has yet reached the market and none are likely to in the next few years. They face a series of major barriers to further expansion, including, the fact that most clinical research is still at an early stage, that no viable business model for their commercial

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exploitation has been established, the need to create a cell processing service infrastructure, major controversy about the use of embryonic material and the lack of any regulatory framework.

Each of these technologies face very significant problems at present and are unlikely to enter the market in anything other than first proof of principle products in the near future.

6.2 Factors shaping the adoption of genomic medicine in the UK

In addition to the analysis of specific technologies, Chapter 5 described the broader environment in the UK, which is shaping the innovation process and the development, diffusion and use of emerging medical technologies. This analysed important changes that are going on under a number of heading and this section will briefly summarise the main ways in which these changes may impact on the development of genetic and biological technologies.

6.2.1 The changing pharmaceutical industry

A continuing focus on blockbuster drugs - The need for high rates of growth, large markets and high profitability will continue to push the pharmaceutical industry to develop blockbuster products for the treatment of common conditions with large international markets. It is far from certain that there will be sufficient financial incentive to support the creation of personalised medicines, such as stem cell therapies and pharmacogenetics.

Focus on chronic diseases management - Continued attention will be given to the treatment of chronic conditions, such as neurodegenerative disorders, cancer and heart disease, and an increasing emphasis on early diagnosis. These diseases have historically been poorly served by conventional small molecule drugs and are a major focus of genetics and related research.

The impact of new technologies - The pharmaceutical industry is heavily committed to investing in biology based R&D. Although its main products are likely to remain traditional small molecule drugs rather than biologicals, it seems likely that the industry will continue to invest heavily in genomic technologies in the hope it can create the new generation of advanced high value medicines. The trend towards R&D outsourcing to the biotechnology industry will reinforce this trajectory.

Taken together this suggests that the pharmaceutical industry will continue to invest heavily in genetic and biological technologies, especially those that are close to its established product focus. However, significant commercial uncertainty surrounds the development of drugs and diagnostics for segmented drug markets. As a consequence, there may be a case for public policy intervention to steer and support technologies that offer clear public health benefits through a mixture of incentives (tax credits, market exclusivity etc.) and tighter regulation (changes in drug labelling – see below).

6.2.2 The changing pharmaceutical market place

The regulation of the UK drugs market - It seems unlikely that changes in the regulation of the price of prescription drugs, the reform of community pharmacy or the shift to OTC medicines will have any significant impact on the development and diffusion of new genomic medicines. Product price at launch can be set by manufacturers and most of these new drugs or diagnostics are likely to be expensive. Furthermore, as Table 6.3 shows very few of these technologies will be available in primary care settings and none are likely to be offered as OTC products in the near future.

Table 6.3 The likely clinical settings for the use of different genetic and biological technologies.

Technology	Pharmacy/ OTC	Primary care	Secondary care	Tertiary care
Genetic testing (monogenic)				+
Therapeutic proteins		+	+	+
Monoclonal antibodies			+	+
Pharmacogenomic drugs			+	+
Pharmacogenetic drugs/tests		+	+	+
Molecular biomarkers		+	+	+
Genetic testing (common)			+	+
Stem cells (adult)				+
Gene therapy			+	+
Cancer vaccines			+	+
Stem cells (embryonic)				+

Direct-to-consumer (DTC) marketing - The increasing emphasis on DTC marketing is unlikely to have a direct impact on the demand for new genome-based drugs in the UK, as TV advertising is still banned. However, patient groups have been successfully mobilised to support the wider adoption of new 'high tech' products, such as beta interferon and Glivec. The use of the internet to promote genetic testing raises important questions about potential mis-selling and consumer protection. However, regulatory authorities are seeking to outlaw most direct sales of genetic tests and at present there is little evidence of consumer demand for these services.

6.2.3 The changing NHS

The modernisation of health services - The introduction of National Service Frameworks and NICE appraisals and guidelines are proving to be an effective mechanism for the development of services and the diffusion of best practice. This is likely to significantly increase demand for specialist therapies if they can be shown to add value and be cost-effective, including therapeutic proteins (beta interferon), monoclonal antibodies (Herceptin) and pharmacogenomic drugs (Glivec).

The development of genetic services - Recent policy initiatives on genetics should help the adoption of several genetic and biological technologies, through the commissioning of new genetic services, the development of service infrastructure and further professional training. In particular, the reform of NHS genetic laboratory

services is likely to have a significant impact on the future growth of pharmacogenetics and genetic testing for both monogenic and common conditions.

6.2.4 Changing professional practice

A new role for pharmacy – Whilst the changing role of community pharmacy is likely to provide greater patient access to many established medicines, it is unlikely to have a significant impact on the use of new genetic and biological technologies as these are mainly used in secondary and tertiary care. Hospital pharmacists may play a greater role in the application of some of these emerging therapies, but this is unlikely to have a major impact on demand.

The move to evidence based medicine – Like all new medical technologies, genetic and biological products will increasingly be judged in terms of clinical utility and cost-effectiveness in relation to established procedures. Although they are likely to be given greater scrutiny by agencies such as NICE, the recent experience of Glivec and beta-interferon suggest that this will not necessarily restrict their diffusion.

6.2.5 Changes to the regulation of new medicines

The oversight of human genetics research – A number of the technologies described in this report, notably disease genetic testing, pharmacogenetics, stem cell therapy and gene therapy, are surrounded by a number of important ethical debates. Recent moves to strengthen the formal oversight of human genetics research in the UK, through the creation of the HGC and other bodies, may play an important role in resolving outstanding ethical debates and ensuring public confidence in genetics and related technologies.

The regulation of medicines and medical devices in Europe and the UK – Regulatory authorities are often blamed for placing unnecessary burdens on innovators and slowing down the pace of chance. However, there is little evidence to suggest that the EU centralised approval process for biotechnology products has been significantly slower than its international competitors. There still remains regulatory uncertainty about the introduction of pharmacogenetics and the introduction of a number of products based on cell processing (e.g. some forms of stem cell therapy, cancer vaccines and gene therapy). Furthermore it remains unclear to what the extent clinical validity and utility will have to be shown with regard to new genetic and pharmacogenetic tests. However, regulators are already playing a key role in promoting the adoption of pharmacogenetics and may be the main driver for the adoption of this technology if they make some form of companion diagnostic testing mandatory for many products.

6.2.6 Government support for the development of innovative health technologies

Policies to promote science, technology and innovation – A clear commitment has been given to promote the further development of innovation in the NHS and the growth of the UK biotechnology industry. These have been articulated in a coherent series of policy measures that seek to increase funding and strengthen both the science base and the infrastructure for undertaking clinical research. These should help

facilitate the process of translating basic research into viable new technologies and the creation of a clinical evidence base.

In summary, it appears that there are a number of competing and cross cutting factors that are helping shape the terrain in which the development and diffusion of new genetic technologies is taking place. However, most of these forces are operating to promote innovation in this area, with increased investment from the pharmaceutical industry, high product prices, the development of related health service infrastructures, a liberalising of professional working practices, a permissive regulatory environment and measures to promote clinical research and development. The only factor that has been seen to inhibit the diffusion of innovative 'high tech' medicines is the working of NICE, but even here initial guidance restricting the use of several new products on the basis of lack of added value/ cost-effectiveness was overturned and a number of its measures have promoted the diffusion of new technologies for specific applications. It therefore appears that the overall environment in the UK is very favourable for the discovery and development of new genetic and biology-based therapies and diagnostics.

6.3   Expectations and innovation in genomic medicine

As highlighted in the introduction, the field of genomic medicine is marked by high hopes for its future. These expectations have been created to a greater or lesser extent by all the key stakeholder groups involved in biomedicine, including scientists, entrepreneurs, investors, clinicians, industry, policy makers, the media and patient groups. This report has attempted to present a detailed analysis of the current state of development of the key emerging technologies in this field and has used the available empirical evidence to assess their prospects for further growth in the medium term. Whilst this is only ever going to provide a partial picture, it none the less places some limits on what it is realistic to expect.

Significantly, it appears that there will be a continuing, but modest, stream of new medicines and diagnostics reaching the market, in particular, therapeutic protein drugs and genetic tests for monogenic disorders. There may also be a small number of new pharmacogenetic drugs/tests, genetic and biomarker based diagnostics for common conditions, adult stem cell therapies based on HSCs and pharmacogenomic drugs, such as Glivec. However the medium term prospects for gene therapy, cancer vaccines and embryonic stem cell therapies are relatively poor and few new products are likely to be launched in the next 3-5 years. The only exception to this overall picture is monoclonal antibodies, which look set to undergo a period of sustained expansion.

Taken together it is clear that this level of progress, whilst welcome, falls a long way short of the high expectations mentioned in the introduction. Does this mean that genetics has 'failed to deliver'? Or have expectations been unrealistic? The latter appears to be a more compelling explanation.

The dynamics of expectation in medical innovation

A number of academic studies in recent years have examined the role of expectations in driving biomedical innovation (e.g. Hedgecoe and Martin, 2003). Rather than

seeing 'hype' as something that has to be disregarded in order to find the 'real' state of play, studies of the dynamics of expectations see these high hopes as playing a central part of the process of bringing a new biomedical technology into being. High expectations are required to mobilise the very significant human, financial and organisational resources needed to undertake innovation in this area. Often these major commitments have to be sustained over many years, with little immediate prospect of success. For example, investors need to have a realistic chance of getting a high return in order to take the risks of financing novel projects. Clinicians and patients need to feel that the risks and sacrifices they are taking will ultimately lead to new cures. In this sense, high expectations are integral and, to some extent, an essential part of the process of developing new genetic technologies. However, they can cause major problems if they are very unrealistic, as false hopes may distort funding and research priorities and ultimately lead to professional disappointment and public disillusionment. It is therefore important to ensure that there is some linkage between public expectations and progress in the laboratory and clinic.

At the heart of the dilemma of managing realistic expectations lies another problem concerning the model of innovation used to guide investment and policy. Much of the language of genetic and biotechnology involves the idea that we are witnessing some sort of 'revolution' in the way in which medicine will be conducted in the future (Nightingale and Martin, 2004). Implicit in this is a model of innovation, which sees the translation of scientific advances into working technologies and new clinical practices as largely unproblematic. In effect, medical technologies are little more than the appliance of genetics and other biological sciences. However, the 'revolutionary' model of technical change in medicine is not supported by the evidence. Instead, as outlined in this report, the process of taking new scientific knowledge and using this to create safe and efficacious medicines and diagnostics is a long and slow process. For example, it has taken nearly 30 years from the creation of the first monoclonal antibody to see a mature technology that can be used to generate a series of important therapies.

Therefore, in order for effective public policy to be developed in the field of genomic medicine, two things need to change; firstly, a more realistic set of expectations about the speed and scale of innovation needs to be adopted by all stakeholder groups; and secondly, a different model, which views biomedical innovation as a slow and incremental process, should be used to inform public discourse and policymaking. In general, it is not the lack of public support, adverse media reports or excessive regulation that holds back the development of new medicines, but the very significant scientific and technical problems involved.

6.4 Realising the potential of genomic medicine – implications for pharmacy

Given the difficulty in accurately predicting which technologies may be successfully developed in coming years, it is perhaps better to establish a set of general guidelines, rather than a detailed list of the possible implications for pharmacy. This report has argued that biomedical innovation in the clinic is best understood in largely incremental terms. From this perspective, new technologies and techniques have to be adopted in routine day-to-day practice. They will therefore only succeed if they can be successfully integrated into established and emerging local services, technical and

organisational infrastructures, patterns of professional work, and governance regimes. In this sense, the development and introduction of genomic medicine is best understood as a process of co-evolution or co-development, in which new technologies shape and are shaped by the broader environment in which they operate. For example, the further adoption and diffusion of genetic testing will depend not only on the discovery of robust and validated clinical associations, but also on the resolution of important ethical debates, the creation of an appropriate IT and laboratory infrastructure, and the training of counsellors and other staff involved in delivering tests. Without each of these being in place it will be impossible to expand testing much beyond their existing service base.

If this model of technical change is adopted, and it is implicit in the thinking behind the Genetics White Paper, then the emphasis of policy is not simply on anticipating the impact of new genetic technologies (so called technology push), but on helping them come into being in ways that improve public health and enhance the role of healthcare professionals. In particular, this will involve:

- Translating scientific research findings into working technologies and new clinical practices;
- Building NHS capacity and developing new services;
- Creating new technical and organisational infrastructures, in areas such as genetic testing;
- Increasing professional knowledge and training;
- Establishing new governance regimes.

The pharmacy profession can play an important role in each of these areas through greater participation in translational research and development, involvement in local and national service planning, the design of infrastructure, enhancing professional training in the broad area of molecular medicine, and being fully involved in the social, ethical and clinical debates that inform the creation of regulations.

Based on the analysis presented in this report, and summarised in Table 6.3, the main genetic technologies likely to affect community pharmacy in the medium term are therapeutic proteins, pharmacogenetic drugs and tests, and new molecular biomarkers. Of these, pharmacogenetic tests and biomarkers of drug response are likely to have the most significant implications for pharmacy. As a consequence, the profession's response to the challenges surrounding the introduction of this technology could form a model for how it might engage with these innovations more generally. Taking this as a case study and using the principles outlined above, the following policies might be adopted relating to pharmacists:

- ***Translating scientific research findings on pharmacogenetics into working technologies and new clinical practices*** – Pharmacists are already playing an important role in clinical research in this area through their involvement in clinical trials and various initiatives funded under the Genetics White Paper. In addition, it is essential to involve the profession in research that examines the drivers and barriers to the clinical adoption of this technology, and assess the training and information needs of staff responsible for the front line use of pharmacogenetic tests in both hospital and community settings.

- ***Building NHS capacity and developing new services in pharmacogenetics*** – The Genetics White Paper has set out a number of initiatives to mainstream genetics in the NHS, including primary care, and to pilot near patient testing. It is essential that pharmacists are involved in these policies. In addition, other specific initiatives related to developing pharmacogenetics services could be taken, including piloting different service delivery models based on a range of genetic tests (e.g. CYP testing for drug metabolism in community pharmacy) and expert systems to support prescribing decisions.

- ***Creating new technical and organisational infrastructures to support pharmacogenetic testing*** – Considerable investment is being made in strengthening NHS genetic testing services through the formation of the UK Genetic Testing Network. If pharmacogenetics is going to be widely adopted in primary care, this will require the successful design and roll-out of appropriate infrastructure to support community based genetic testing, prescribing and post-marketing surveillance. This will probably involve a period of experimentation and trial and error. Pharmacists will therefore need to be involved in the design and development of a range of different models and systems for service delivery adapted for various settings and applications.

- ***Increasing professional knowledge and training of pharmacogenetics*** – Whilst the pace of introduction of new genetic technologies and services may end up being slower than anticipated, it is clear that a number of the technologies described in this report will ultimately enter practice over the next few decades. As a consequence, pharmacists currently receiving their initial training are very likely to use some of these innovations during their professional life. So whilst realistic expectations need to be maintained, it is also essential that professional training and ongoing validation involves a detailed knowledge of molecular medicine in general and pharmacogenetics in particular. The professional development programmes for pharmacists being introduced by the NHS Genetics Education and Development Centre, which covers issues such as the counselling of patients on the implications of tests results, is a good example of what is required.

- ***Establishing new governance regimes to control the use of pharmacogenetic testing*** – A number of important social and ethical issues remain unresolved in relation to genetic testing and its application to pharmacogenetics. These include the issues outlined in Chapter 2. Pharmacists and their professional bodies should be actively involved in these debates to ensure their experience and expertise is drawn on, and that the profession fully supports the effective governance of these technologies. Furthermore, the profession should play an active part in the wider public debate about the introduction and impact of new genetic knowledge, and help foster the creation of more realistic expectations in this domain.

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