



The ethics of patenting DNA

a discussion paper

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BIOETHICS

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The terms of reference are as follows:

- 1 to identify and define ethical questions raised by recent advances in biological and medical research in order to respond to, and to anticipate, public concern;
- 2 to make arrangements for examining and reporting on such questions with a view to promoting public understanding and discussion; this may lead, where needed, to the formulation of new guidelines by the appropriate regulatory or other body;
- 3 in the light of the outcome of its work, to publish reports; and to make representations, as the Council may judge appropriate.

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Foreword

The Council convened a group of experts to discuss the ethics of patenting DNA in June 2000. At the time, the sequencing of the human genome was close to completion. There was also increasing discussion about the ethical and social issues raised by patenting genes.

The aim was to produce a short Discussion Paper after three or four meetings in a matter of months. That the process took two years and nine meetings testifies to the difficult and complex nature of the issues that were raised. I am deeply indebted both to the group whom we brought together and to the many other individuals who generously brought their expertise to bear on what have been some of the most testing questions that the Council has yet considered. I thank them all.

The Council hopes that this Paper will help to clarify various issues and encourage further discussion. The Council also hopes that the conclusions and recommendations will provide guidance for policy makers and others who have to make difficult judgements about patents relating to DNA.



Ian Kennedy
Chairman

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The ethics of patenting DNA

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The ethics of patenting DNA

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Executive Summary

The remarkable development and application of new genetic technologies over the past 25 years has been accompanied by profound changes in the way in which research is commercialised in the life sciences. Many thousands of patents which assert rights over DNA sequences have been granted to researchers across the public and private sector. In general, we acknowledge the benefits that have accrued to society from the patent system, but we ask whether the application of the patent system to DNA sequences is achieving its goals, namely the stimulation of innovation for the public good, and the rewarding of people for useful new inventions.

We note that many patents that assert rights over DNA sequences have already been granted but are of doubtful validity. The effects of many of these patents are extensive, because inventors who assert rights over DNA sequences obtain protection on all uses of the sequences.

We conclude that in the future, the granting of patents that assert rights over DNA sequences should become the exception rather than the norm. The patent system currently regards DNA sequences as eligible for patenting. However, as computational techniques replace cloning as the main route to identifying genes, we consider that the issue of the eligibility for patenting of DNA sequences needs to be reopened. Even if DNA sequences are considered eligible for patenting, they must then satisfy the criteria of being novel, inventive and useful. We consider that the application of these criteria to DNA sequences has not been sufficiently stringent. We note, further, that the fact that DNA sequences are essentially just genetic information distinguishes them from other chemical compounds, with regard to the patent system.

We distinguish four different uses to which DNA sequences can be put: in diagnostic tests based on genes, as research tools, in gene therapy and for the production of therapeutic proteins. We conclude that patents that assert rights over DNA sequences and their uses are, in some cases, supportable, but in others, should be treated with great caution.

Diagnostic tests

- **We recommend that the criteria already in place within existing patent systems for the granting of patents, particularly the criterion of inventiveness, be stringently applied to applications for product patents which assert, inter alia, rights over DNA sequences for use in diagnosis. We recommend that the European Patent Office (EPO), the United States Patent and Trademark Office (USPTO) and the Japan Patent Office (JPO) together examine ways in which this may be achieved.** If this recommendation is implemented, we expect that the granting of product patents which assert rights over DNA sequences for use in diagnosis will become the rare exception, rather than the norm.
- We consider the grant of use patents for diagnostic tests and **conclude that the protection by use patents of specific diagnostic tests which are based on DNA sequences could provide an effective means of rewarding the inventor while providing an incentive for others to develop alternative tests.**
- We consider that, in the case of patents that have been granted for diagnostic tests based on genes, compulsory licensing may be required to ensure reasonable licensing terms are available to enable alternative tests to be developed.

Research tools

- **We consider, that in general, the granting of patents which assert rights over DNA sequences as research tools should be discouraged.** We have taken the view that the best way to discourage the award of such patents is by stringent application of the criteria for patenting, particularly utility.

Gene therapy

- **We consider that once a gene which is associated with a disease is identified, the use of the relevant DNA sequences in gene replacement therapy, to alleviate the effects of mutations in that gene, is obvious (particularly when such use is claimed on a purely speculative basis). Therefore, we recommend that protection by product patents should seldom be permissible.** We believe that patent protection should be concentrated on developing safe and effective methods of appropriate gene delivery. This is where the real inventiveness and investment will be required, rather than in simply defining the sequence of the genes to be used in treatment.

Therapeutic proteins

- **We take the view that while rights asserted over DNA sequences which are used to make new medicines that are therapeutic proteins are generally acceptable, they should be narrowly defined. By this we mean that the rights to the DNA sequence should extend only to the protein described.**

We consider that the adoption of the recommendations that we put forward here will serve to guide patent offices and the courts to a more rational use of the system which reserves patent protection for those patents that assert rights over DNA sequences that reflect a significant contribution by the researcher.

Chapter

Introduction

1

Introduction

- 1.1 The study of biology was radically transformed by the discovery in 1953 of the structure of DNA, which is the genetic material of living organisms (see Box 1.1). Since then, scientists have made considerable advances in understanding how DNA works, and how differences in DNA lead to differences between people. In 1990, the Human Genome Project was established to co-ordinate research that aimed to identify all the genes in human DNA, and to determine the order of the three billion chemical base pairs that make up human DNA. In 2001, the draft map of the human genome was published, which at least partially identified the majority of the estimated 30,000-40,000 human genes. Many of these genes play a role in human diseases and disorders. Their identification may be a first step in the development of new diagnostic tests and treatments. Research in the rapidly expanding field of genomics aims to discover the biological function of particular genes, and how sets of genes and proteins work together in health and disease. Research is also focusing on identifying and understanding the proteins produced by the genes.
- 1.2 Research into the sequence of the human genome has been undertaken jointly by publicly-funded bodies such as universities, charities, foundations and research institutes, and by privately-funded industrial organisations. Two versions of the map of the human genome sequence were published by the two communities of researchers, the data from the publicly-funded research having been incorporated into the privately-funded version.¹ The public sector project was conducted against the background of a strong commitment to the public sharing of, and access to data. All publicly-funded data regarding the draft sequence were placed on public databases as they were generated each day. In contrast, industry has generally treated DNA sequence data as confidential.
- 1.3 The protection of knowledge about human genes has primarily been achieved through the patent system, though other devices such as trade secrecy and confidentiality have also played a role.² The patent system is a long-established method of encouraging people to develop new and useful objects by ensuring that they are able to capitalise on their inventions. A patent confers on the inventor an exclusive right for a limited period of time (usually 20 years) to prevent others from exploiting the invention. Patents have been used for over a century to protect a wide range of inventions including new medicines, new materials and new machines. Naturally-occurring phenomena such as electricity or wild species of plants or animals are not regarded as inventions but as discoveries and thus are not eligible to be patented.
- 1.4 The substantial increase in the rate of patenting of DNA sequences by researchers in both the public and private sectors over the past six years has led to considerable discussion and debate about the acceptability of this practice.³ The issue has been debated in numerous arenas and at

¹ The public sector human genome project published the sequence in *Nature* (see Lander ES et al. Initial sequencing and analysis of the human genome. *Nature* 2001 Feb 15;409(6822):860-921); while the private sector project undertaken by Celera Inc, a US genomics company, was published in *Science* (see Venter JC et al. The sequence of the human genome. *Science* 2001 Feb 16;291(5507):1298-302).

² The importance of secrecy as a method of protecting knowledge was highlighted by a recent survey of academic geneticists in the US which found that 35% of researchers felt that there had been a decline in the sharing of data in the past ten years. It also found that researchers who had been engaged in the commercialisation of university research were significantly more likely to withhold data from other researchers. The study concluded that the withholding of data in the field of genetics, though not widespread, was nonetheless affecting essential scientific activities such as the ability to confirm published results (see Campbell EG et al. Data withholding in academic genetics: evidence from a national survey. *JAMA* 2002;287:473-80).

³ See World Health Organisation. Advisory Committee on Health Research. Genomics and World Health. 2002. http://www3.who.int/whosis/genomics/pdf/genomics_report.pdf (7 Jun 2002).

Box 1.1: **Proteins, genes and DNA**

Genes are discrete segments of DNA molecules that contain the information necessary for producing specific proteins. DNA is made up of a string of units called nucleotides. The main component of these nucleotides are bases, which are arranged in a specific sequence. There are four different bases in DNA: adenine (A), thymine (T), cytosine (C), and guanine (G). These bases are bonded together in pairs, A with T and C with G, to make the DNA double helix. Genes can range in size from fewer than 100 base pairs to several million base pairs and are separated from one another by spacer DNA. The base sequence is the crucial feature of the gene. It is this sequence that carries the genetic information essential for the synthesis of an RNA molecule that may subsequently direct the synthesis of a protein molecule or may itself be functional in the cell. This process is called gene expression; it has two stages. The first stage in gene expression is transcription (the process by which the gene's DNA sequence is copied into RNA) and the second stage is translation (the process by which RNA directs the synthesis of a protein). Proteins are composed of amino acids and are the molecules that carry out the work of the cell. All the DNA in an organism is called the genome.

a range of levels. Patent law and practice has developed as a result of these debates. There remain, however, questions about the application of patent law with respect to DNA sequences and concerns about the potential consequences for society of allowing such patents. In 2000, the Nuffield Council on Bioethics convened a Round Table Meeting with the aim of producing a Discussion Paper that would clarify the issues raised and propose ways of taking the debate forward. This Paper is the result of nine meetings of the Round Table group, who were helped in their deliberations by experts in relevant fields from around the world. The subject which this paper tackles is necessarily technical and complex. It will be most readily accessible to those with an existing interest in, and knowledge of, genetics and the patent system.

Background to the current debate

- 1.5 Chemical compounds including medicines, chemical processes such as the polymerase chain reaction (PCR)⁴ and medical devices such as the diagnostic test for hepatitis C have been the subject of patents for some time. Living organisms have also been the subject of patents. The modification of living organisms through genetic engineering in the 1970s and 1980s opened up new possibilities for the development of novel products and processes. By inserting foreign or synthetic genes directly into a bacterium, scientists were able to contemplate the creation of new drugs based on human genes, new crops and transgenic animals with new or enhanced properties.
- 1.6 Such developments rapidly led to an appreciation of the commercial possibilities arising from genetic modification and the advantages of protecting developments through the application of the patent system. Several hundred small biotechnology companies were established during the late 1970s and 1980s in the US to develop and apply the new genetic technologies. Many were founded within universities by entrepreneurial academics and later 'spun out' into the industrial sector. These developments in the life sciences, which were mirrored in other technologies, eroded the relatively clear divide between the publicly-funded sector of universities, research institutes and foundations, and industry. In 1980, the Bayh-Dole Act was passed in the US, which allowed universities and other public institutes and their employees to seek patent protection for their inventions and retain the royalties.

⁴ PCR is an *in vitro* method for generating unlimited copies of any fragment of DNA. PCR is useful for the characterisation and analysis of regions of DNA which lie between two regions of known sequence.

The same practice has, to a greater or lesser extent, been encouraged by the governments of many other countries. Thus the development of the new genetic technologies was accompanied by a changing culture in universities, where the pursuit of profit and patents took place alongside the more conventional academic activities of scholarship and the writing of books and scientific papers. These developments, encouraged by governments, have not been confined to the US. Universities around the world now have offices for intellectual property to encourage and facilitate the gaining of patent protection for the inventions of their faculty. Today, the owner of the greatest number of US patents that assert rights over genes is the US government, most of which have been generated by the National Institutes of Health (NIH) Intramural Research Program.⁵

- 1.7 Over the past 20 years, large numbers of genes, sections of genes and the proteins they produce have been the subject of several thousand patent applications. Many patents have been granted. The identification and cloning of genes that produce therapeutic proteins has led to the development of a number of new medicines based on human proteins⁶, whilst the identification of genetic mutations that cause disease has been widely applied in the development of diagnostic tests for relatively rare diseases. Patents that assert property rights over DNA sequences have been granted in both these areas. Many pharmaceutical companies have invested in substantial research programmes to apply genetic knowledge to the process of drug discovery. With the completion of the sequencing of the human genome, many more patent applications for new drugs, vaccines and diagnostic tests involving the use of the estimated 30,000 - 40,000 human genes and their expressed proteins can be expected.⁷ The market for medicines (in the form of therapeutic proteins) and vaccines is already significant.
- 1.8 Over the past decade, the idea that a gene or DNA sequence can be the subject of property rights as part of an invention and that the rights to the use of this alleged invention might rest with a single owner, such as a company, has attracted increasing criticism around the world. Researchers, clinicians, non-governmental organisations (NGOs), and religious groups have opposed, in particular, the idea that a DNA sequence can constitute part of an invention and therefore be claimed as property by the patent owner. This opposition seems to arise from anxiety about what might be termed 'private appropriation of the genetic commons'. We discuss this concern further in Chapter 3.
- 1.9 Concerns have been articulated relating to the effects of awarding exclusive rights, albeit time-limited, in this field. Four potential problems that may arise as a result of patents that assert rights over DNA sequences being granted are:
- 'preventing or hindering development of new or improved medicines and treatments;
 - limiting access to healthcare by increasing the cost of diagnostic [tests] and treatment for certain diseases;

⁵ Cook-Deegan R. Gene patents - why secrecy is destructive to innovation. In: Commercialization of genomics: challenges and opportunities. Cambridge, MA: Cambridge Healthtech Institute; Dec 2001. p. 59. Furthermore, some public sector grant-giving agencies require the researchers they fund to seek protection for their intellectual property.

⁶ For example, erythropoietin (Epo), granulocyte colony-stimulating factor (G-CSF), tissue plasminogen activator (t-PA) and human growth hormone.

⁷ In 2000, the Guardian newspaper published a report on patenting which included estimates of the number of patent applications filed that assert property rights over DNA sequences, based on research commissioned from GeneWatch UK. The newspaper stated that 'Patents are already pending or have been granted on more than 50,000 genes and partial gene sequences in living organisms.' (See Meek J. The race to buy life. In: The Guardian. 15 Nov 2000. <http://www.guardian.co.uk/genes/article/0,2763,397827,00.html> (30 May 2002).)

- exploiting information and materials and inhibiting their free exchange between researchers;
- involving parties in extensive and costly legal battles.⁸

Conversely, it has been argued that patents on DNA are necessary to stimulate investment in research and development on new healthcare products and processes, to assure protection in the market for new products and to facilitate the disclosure of scientific information. This paper critically assesses these arguments.

- 1.10 The joint statement which the Prime Minister of the UK, Tony Blair, and the President of the US, Bill Clinton, made on 14 March 2000, reflected the tension between the calls for openness and access to data on the human genome and the calls for the protection of data to facilitate commercial development. The statement declared that 'raw fundamental data on the human genome, including the human DNA sequence and its variations should be made freely available to scientists everywhere'.⁹ But, it also recognised the importance of intellectual property, noting that 'intellectual property protection for gene-based inventions will also play an important role in stimulating the development of important new healthcare products'.

Background to this Discussion Paper

- 1.11 Various bodies have been or are engaged in work to assess the ethical implications of patenting DNA and to consider reform of current patent systems. The United Nations, through its Convention on Biological Diversity signed in 1992, placed strong emphasis on the fair and equitable sharing of benefits arising from the use of genetic resources. The Council of Europe has since proposed collaborating with the European Union (EU), World Intellectual Property Organisation (WIPO), Food and Agriculture Organisation, World Trade Organisation (WTO) and United Nations Educational, Scientific and Cultural Organization (UNESCO) to discuss a suitable alternative system of protecting intellectual property in relation to biotechnology which would meet the aims of the Convention on Biological Diversity and global interests, both public and private. Work is also continuing on the section of the Council of Europe's additional protocol of the Convention on Human Rights and Biomedicine devoted to the consideration of issues raised by the human genome.

- 1.12 The aim of this Discussion Paper is to examine the issues relating to genetics and intellectual property, particularly those that concern human healthcare and research related to healthcare. The objectives of the Round Table Meeting were:

- to examine ethical and legal issues within the current regulatory framework;
- to provide an ethical framework and policy recommendations to assist policy-makers and others, particularly the courts, patent lawyers and patent offices.

The Round Table Meeting did not consider a number of related issues such as the question of access to medicines in developing countries, or wider questions about intellectual

⁸ Patenting genes - stifling research and jeopardising healthcare. GeneWatch UK Apr 2001.

⁹ Prime Minister Blair, President Clinton. Joint statement to ensure that discoveries from the human genome are used to advance human health. 14 Mar 2000. <http://www.patent.gov.uk/about/ippd/notices/genome.htm> (13 May 2002). The Blair/Clinton statement was compatible with the Bermuda statement which set out guidelines for the release of DNA sequence data from genome centres participating in the international Human Genome Project. Participating centres were required to release their data from high-throughput screening on a daily basis.

property and the developing world. Nor did the group consider the patenting of DNA outside biomedicine, for example in relation to food and crops.

- 1.13 The structure of the Discussion Paper is as follows. Chapter 2 describes the justification advanced for the patent system and explains how the system functions. Chapter 3 explains how patents can assert rights over DNA sequences and examines the question of whether DNA should be patentable. It also summarises the current legal situation in the UK, Europe and the US, with regard to the patenting of DNA sequences. Chapter 4 contains five case studies that illustrate the possible effects of allowing patents that assert rights over DNA sequences. Chapter 5 considers the effects of such patents in more detail and proposes ways of modifying the patent system to ensure that it continues to work for the benefit of all. Chapter 6 summarises our conclusions and recommendations.

Chapter

2

The patent system

The patent system

2.1 Before turning to the question of patents involving genes, it is important to discuss the patent system in general. In this chapter, we explain what patents are, consider the justification for the patent system, and set out brief details about how the patent system works.

Box 2.1: About patenting

What is a patent?

Patents are exclusive rights granted for a limited period of time by states through their legal systems to inventors to prevent others from exploiting the patent holder's invention. Patent applications contain *claims* which set out the precise nature of the protection. The commercial exploitation of something within the scope of the claim of a patent that has been granted, without the authorisation of the owner of the patent, is called *infringement*. Patent claims are normally drafted to ensure that they cover more than exact duplication of the inventor's work.

Owners of patents will often themselves exploit commercially the inventions they have patented (for example, by manufacturing a medicine), but possession of a patent alone does not require this. It is possible to have a patent but not to enforce or use it. Many patents are also licensed by the owner to other parties for commercial use. A common misconception is that a patent gives an inventor an absolute right to exploit the invention. It does not. Exploitation will depend on whether others have patents which overlap with the subject matter of the invention, and will be subject to other existing laws, such as those concerning health and safety.

What are the criteria for granting a patent?

For a patent to be granted, the followed criteria must be satisfied:

- the claimed invention must be eligible for patenting;
- it must be novel;
- it must be inventive or non-obvious;
- it must be useful or have industrial application;
- it must be fully disclosed in the patent application.

In addition, to be eligible, the invention must not be contrary to morality or *ordre public*.

What is the process for granting a patent?

The process of granting a patent involves several steps (these are described in more detail in Appendix 1). Firstly the patent is filed, i.e. the patent application is submitted to a patent office. The next step is substantive examination in which a patent examiner determines whether or not the patent application is allowable. If it is found to be allowable the applicant is awarded the patent i.e. the patent is granted or issued. However, it is still possible for the patent to be challenged or opposed by a third party, either in court or via a patent office. If the opposition is found to be well-founded then the patent may be revoked, although this decision may be appealed.

How are patents licensed?

Licensing of patents is in some ways similar to the leasing of physical property in that it allows the granting to another party of the right to use the patented products or process on defined terms. Licences may be exclusive or non-exclusive. The former gives the licensee the exclusive right to use the licensed patent. A non-exclusive licence means that other licences can be granted and that the owner of the patent can also use the invention.

Intellectual property rights

- 2.2 Patents are a form of intellectual property (IP) which confer rights over an invention on its inventor (see Boxes 2.1 and 2.2). These are privileges which enable inventors to capitalise on their invention, subject to wider constraints such as public interest and the IP and rights of others. Other forms of IP include copyright¹, registered designs and trademarks.
- 2.3 The overall goals of the patent system are to stimulate innovation for the public good and to reward people for useful new inventions. The patent system aims to achieve this by allowing inventors exclusive rights for a limited period to exploit their inventions, while at the same time promoting competition and innovation by ensuring that such inventions are fully disclosed to the public. The system is intended to balance the interests of the public with those of the inventors. Inventors have an interest in being rewarded for their effort, for example, by being able to recoup financial investments in research and development and to profit from their invention.
- 2.4 The public interest is harder to specify, but it is primarily a matter of making it possible for individuals to further their own interests as far as circumstances and the interests of others

Box 2.2: Property rights

Since patents are a form of property, the rationale for their justification lies within the justification of property rights in general. There are essentially two approaches to justifying property rights. The first argues that there are no 'natural' property rights, but that such rights are basically a matter of public convention. This leads to a utilitarian justification of property rights as a system of public rules which provide security and incentives for investment by individual owners of property, but which can and should be adapted wherever the public interest is thereby served. The second approach, famously propounded by Locke, holds that there is 'natural' right to that with which one has 'mixed one's labour'.¹ This can be understood most easily in the context of ownership of land: the idea is that by cultivating an area of previously 'unowned' land, and thereby 'mixing one's labour' with it, one can acquire property rights over it. This second approach to justifying the ownership of land and other 'natural' resources is much disputed; but it may be said to be much more acceptable in the context of IP, since it does seem right that someone who creates something new, for example a novel, sculpture or painting, has rights such as copyright, over that which is created. In a similar way, this approach can be applied in the context of industrial or technological inventions to justify the patent system.

These two approaches are not exclusive; in particular the second approach can be readily combined with the utilitarian considerations to yield the view that the rights of inventors may be qualified and circumscribed in ways that contribute to the public interest.² We accept this combination of the two approaches to the justification of intellectual property rights.

¹ Locke J. An essay concerning the true original extent and end of civil government. 1690.

² For further reading, see Ryan A. Property and political theory. Oxford: Blackwells Publishers; 1984. Waldron J. The right to private property. Oxford: Clarendon; 1988; Nozick R. Anarchy State & Utopia. Oxford: Blackwells Publishers; 1974; Harris JW. Property and justice. Oxford; New York: Clarendon; 1996.

¹ Copyright is an unregistered right that comes into effect as soon as something that can be protected is created and 'fixed' in some way, for example on film, on paper or on the internet. Copyright is used to protect such things as novels, song lyrics, original dramatic, musical and artistic works, sound recordings and films. Copyright protects the way an idea is expressed in a piece of work, but does not protect the idea itself.

permit; in the context of the present discussion, it is the interests of individuals in securing access to new medicines and other products and services that are especially important. An important aspect of the public interest thus understood is the provision of goods which are essentially shared. Public roads and parks are familiar examples of goods of this kind: they are goods which contribute to the interests of individuals, but because they are shared, they are typically provided not by individuals for themselves but by public institutions. Other examples, such as clean drinking water, reliable sewage systems and systems for disease control involve public health institutions. But the main question which concerns us here arises from the role of the patent system. It is in general in the public interest that there be a patent system which promotes inventions such as new medicines and other medical products by providing an incentive in the form of limited monopolies. What remains open to debate, however, is how far the public interest is served when this patent system is applied in such a way that it makes it possible for private companies and other institutions to have an exclusive right to exploit the medical significance of genetic discoveries, albeit for a limited period of time.

- 2.5 In light of the balance between public and private interests that must be achieved by the patent system, it can be seen that the granting of patents might be judged unethical if it would mean that inventors would enjoy a reward that is not commensurate with their contribution, or if the return to society is not commensurate with the benefit enjoyed by the patent owner. The question of the balance between public and private claims which will best promote the public good is taxing; it is this question we address in the remainder of this paper. Before doing so, however, we assess the economic importance of patents in general, and set out briefly how the patent system works.

The economic importance of patents

- 2.6 Two key features of patents are that they stimulate invention and promote the disclosure of inventions, which enables other inventors to learn about them and to develop improvements and alternatives. Patents represent one of the most important incentives for commercial enterprises to undertake research and development, by allowing them to enjoy returns on the generation and application of knowledge. The patent system provides an incentive to invest in the production and application of knowledge by allocating benefits directly to those companies making the investments, and because it grants property rights which recognise an inventor's exclusive right to prevent others, for a fixed term, from making, using or selling an invention based on that knowledge without licence. By contrast, the inability or failure of companies to prevent others from making use of the new developments they generate is an established cause of the failure of commercial enterprises.² Further, as most patents do not relate to major breakthroughs but to technical advances of an incremental nature, patent protection is thought to support the coherent planning of companies' investments and to allow them to make incremental progress. Moreover, because patents facilitate the dissemination of knowledge, they also serve to prevent costly and wasteful duplication of the efforts of researchers.
- 2.7 While patents have been found to be significant in themselves as a component of the market value of companies, it is also true that companies use a wide variety of mechanisms to protect their IP. Indeed, in general, patents are ranked as less important in terms of value to the company than other mechanisms such as secrecy. Patents do, however, have particular

² Hirshhorn R and Langford J. Intellectual property rights in biotechnology: the economic argument. Prepared for the Canadian Biotechnology Advisory Committee Project Steering Committee on Intellectual Property and the Patenting of Higher Life Forms; 2001.

importance in some sectors of commerce. A notable example is the pharmaceutical industry, which is heavily reliant on strong IP protection for a number of reasons:

- i) The costs of bringing a novel medicine to market are substantial and need to be recouped. These costs include the cost of carrying out clinical trials of novel medicines and the regulatory requirements regarding safety.³
- ii) The industry is one which develops products which are easily copied. Without patent protection, any producer could copy a medicine invented and developed by another, and sell it, without having to invest in the necessary research and development.
- iii) Companies need to recoup the costs of investments in research and development which do not succeed in producing a new product: only one out of every 5,000 compounds discovered eventually reaches the market place as a novel medicine.⁴

2.8 This suggests that without patent protection, some novel medicines might never be invented. It is often conceded that, while patents may not always increase innovation, when they do, it is usually in the pharmaceutical and biotechnology sectors.⁵ However, it is also worth observing that despite the economic importance of IP protection to the pharmaceutical industry, the rewards it can accrue from the patent system are not as great as may initially appear. A medicine enjoys 20 years of patent protection, but as most pharmaceutical companies file and receive patent protection for the commercial use of a compound during pre-clinical trials, several years before a medicine is finally marketed, its effective patent life may be reduced by as much as 10-12 years.^{6,7} Moreover, companies generally bring to the market only about one out of every hundred products for which they have obtained patents.

2.9 Small companies engaged in biotechnology, particularly as it relates to healthcare, also rely heavily on IP. The possession of patents helps to attract financing, especially support from venture capital, and assists in the establishment of alliances, enabling companies to share the costs of research and development, or in providing support when a product is put on the market. Some biotechnology companies do not in fact manufacture products, but engage in research with the aim of funding their work and of making profits by licensing their patents and databases. This type of company is currently more common in the US.

2.10 We accept the general view that patents have promoted the public interest by encouraging the development of new medicines and vaccines. This judgement relies on data about the economic importance of patents which are hard to quantify and evaluate, but a thorough economic analysis of the importance of patents in the pharmaceutical and biotechnology sectors is outside the scope of this paper. However, both to do justice to the achievements

³ The Tufts Center for the study of Drug Development estimated the cost of developing a new prescription medicine at \$802 million in a study in November 2001. However, the US national consumer group Public Citizen estimated in July 2001 that the actual after-tax expenditure for developing a new medicine, and taking account of initiatives which fail, was £110 million (see New study expected to significantly overstate drug industry R&D costs. Citizen.org. 28 Nov 2001. <http://www.citizen.org/pressroom/release.cfm?ID=942> (13 May 2002).)

⁴ Spilker BA. The drug development and approval process. PhRMA. <http://www.phrma.org/searchcures/newmeds/devapprovprocess.phtml> (13 May 2002).

⁵ See, for example Hall B. Testimony for the FTC/DOJ (Antitrust) hearings on competition and intellectual property law in the knowledge-based economy. 26 Feb 2002. <http://www.ftc.gov/opp/intellect/020226bronwynhalltext.pdf> (14 June 2002).

⁶ See, for example Bale HE Jr. Patents and public health: a good or bad mix? <http://www.pfizerforum.com/english/bale2.shtml> (13 May 2002).

⁷ However, a supplementary protection certificate which extends a patent for 5 years is often obtained for pharmaceutical products.

of inventors and because of the importance of stimulating innovation, particularly in the pharmaceutical sector, **we conclude that exclusive rights awarded for a limited period are, in the main, defensible and that the patent system has in general worked to the benefit of people. Nonetheless, we consider that in the particular case of patents that assert property rights over DNA, consideration should be given to whether the balance between public and private interests has been fairly struck.** We consider this issue further in Chapters 3-5.

How the patent system works

- 2.11 Within most jurisdictions, patents are granted by specialist patent offices. The offices that are particularly relevant to this paper are the European Patent Office (EPO) and the US Patent and Trademark Office (USPTO). Patent examiners in these offices are responsible for establishing whether an application for a patent meets the criteria for patenting in the relevant jurisdiction although their decisions may be, and often are, challenged. The US and European patent regimes differ in a number of important ways, including the criteria for deciding who is the first inventor of an invention, when a patent application can be filed, and, until recently, when it is published.
- 2.12 The EPO is an international patent-granting authority established under the European Patent Convention (EPC) in 1978 that grants European patents for the contracting states to the EPC.⁸ The EPO is financed by the fees it charges for assessing patent applications and has a large degree of administrative autonomy.⁹ It was established as a result of co-operation in the field of IP between the states of Europe. The European Patent Organisation, for which the EPO acts as the executive arm, currently has 24 member states (at 1 July 2002): these members are the EPC contracting states.¹⁰ A patent in a European country which is a member of the EPC can be obtained either by applying to the national patent office in that country, or by filing an application at the EPO. The effect of a patent awarded by the EPO is to create, for the European member states designated by the applicant, a series of parallel national patents, which are treated as if they had been granted by each national patent office of the designated states. These patents are valid for 20 years, although extensions are possible for patents relating to pharmaceutical inventions and plant products.¹¹ The procedure of applying for and being granted a patent takes an average period of 44 months but can be as long as ten years.¹² In this paper, when we refer to European law, or the patent system in Europe, we refer to those countries that are members of the EPC.
- 2.13 The USPTO examines applications and issues patents, and examines and registers trademarks. It is also funded by the fees it charges for examining patent applications. US patents are valid for 20 years from the date of filing, although extensions of time are possible for patents relating to pharmaceutical and plant protection products. The USPTO has, in the past, been somewhat faster than the EPO in processing patent applications although recently it appears to have slowed down.¹³ The speed at which patent applications

⁸ The majority of patents that assert property rights over DNA taking effect in Europe are granted by the EPO.

⁹ The EPO's operating and investment budgets are funded entirely from fees levied on applications.

¹⁰ These include all the EU countries plus Bulgaria, the Czech Republic, Cyprus, Estonia, Liechtenstein, Monaco, Slovakia, Switzerland and Turkey.

¹¹ Such extensions are authorised under Article 63(2) (b) of the EPC.

¹² How to obtain a European patent. European-patent-office.org. 29 May 2001. <http://www.european-patent-office.org/epo/obtain.htm> (21 May 2002).

¹³ 1999 - 25.2 months, 1998 - 24.4 months, 1997 - 22.9 months, 1996 - 21.5 months (data from the Trilateral patent office website).

can be processed is limited by the availability of patent examiners and it is common for patent offices to have substantial backlogs of unexamined patent applications.¹⁴

- 2.14 At present there are no supra-national or international patents, although there is considerable political pressure to create an EU Patent, or 'Community Patent'.¹⁵ Although there are a number of international patent agreements and the criteria of patentability are in outline harmonised throughout the world, the procedure for processing patent applications varies according to the prevailing regulatory framework. The Patent Cooperation Treaty (PCT), which is administered by the WIPO provides an international central body that enables applicants to seek protection in about one hundred countries worldwide. This procedure gives the applicant the option of obtaining an international preliminary examination report about the patentability of an invention before any costs associated with the procedure for applying for a patent are incurred. Through the PCT procedure, inventors can apply for patents in different countries in one step.
- 2.15 The processing of patent applications by the USPTO and the EPO tends to be lengthy. In the EPO, there is a considerable period of uncertainty, during which the fate of an individual patent is unknown. Between the time of the patent application being filed and the patent being granted, the technology or product can be used, but those who do use it may be subsequently required to pay damages for infringement if the patent is granted.¹⁶ In Europe, once the patent has been granted, the patent holder has a claim against those who have used the invention between the time of publication of the application and the time when the patent was granted. In such circumstances, the patent holder can claim 'reasonable compensation' in circumstances where the other party would be liable under national law for infringement of a national patent (Article 67(2) of the EPC). Under German law the use of an invention, which is covered by a published patent application carries no penalty until the patent is granted. In the US, until recently, the owner of the patents, once granted, have been able to recover compensation only from the date of the grant of the patent, because only then was a patent published.
- 2.16 How do the patent offices decide whether to accept or reject a patent application? The roles of patent examiners at the USPTO and the EPO are broadly similar (see Appendix 1). The patent examiner undertakes a documentary search of the scientific and patent literature and

¹⁴ An important difference between the US system and elsewhere has been that US patents were not published prior to being granted. This led to many patent applications being 'in the system' for up to 10 years before being published. Moreover those applications that were rejected were never published. However, this changed in November 2000 (as a result of the American Inventors Protection Act 1999), and US patent applications are now published 18 months after the date of filing of the application. This change has brought the US further into line with Europe and Japan which already publish patent applications. However, there is a significant exception that can be invoked by those applying for patents in the US: those who declare that they will not file patent applications for their invention in certain countries outside the US (including Japan, Canada, Australia and many European countries) can avoid publication. This option may be useful when inventors need a strategic advantage over their competitors or when there is some doubt about the patentability of the subject matter. In either circumstance, the inventor can retain confidentiality until the patent is granted.

¹⁵ In August 2000 the European Commission formally proposed the creation of a Community Patent, which would allow patent protection to be secured throughout the single market on the basis of a single patent application. Under the Commission's proposal, Community Patents would be issued by the EPO. National and European patents would coexist with the Community Patent system, allowing inventors to choose which type of patent protection would best suit their needs. (Community Patents would allow protection in all the member states, while European patents would cover only those states designated by the applicant). The aim would be to make community-wide protection as simple and inexpensive to obtain and as comprehensive in its scope as the protection granted to competitors in the US and Japan. Implementation of the Community Patent has been stalled by specific points of contention, concerning the future role of national patent offices and their relationship with the EPO, the different languages, and the establishment of a Community Patent jurisdiction.

¹⁶ In general, much higher amounts of damages are permissible in the US. The levels in the UK are significantly lower but higher than those generally prevailing in other European countries.

examines the application to determine whether it meets the criteria for patentability, what is the scope of the protection claimed by the inventor and whether the invention is adequately described in the patent claims. As far as we are aware, under all patent law jurisdictions, a patent office must give a reason why a patent is not granted and specify which patentability requirement(s) was (were) not met. The examiner's role is to make a technical assessment of the application in the light of the law relating to patents. The examiner is not required to consider the social, ethical or economic implications of granting a particular patent except in so far as these concerns are reflected in patent legislation. (See paragraphs 3.44 – 3.48 which consider the 'contrary to morality' or '*ordre public*' clauses.) There are various national and international laws, regulations and treaties that apply to the patent system. A summary of relevant legislation and important legal cases is given in Appendix 2.

Challenging patents

Europe

2.17 Patents granted by the EPO can be challenged by a third party by submitting what is termed an 'opposition' to the EPO within 9 months of the patent being awarded. This can be on any of three grounds:

- the subject-matter of the patent is not patentable according to the terms of Articles 52 to 57 of the EPC;
- the invention is not disclosed in the patent in a sufficiently clear and complete way for it to be reproduced by a person skilled in the art;
- the breadth of the patent's subject-matter exceeds the content of the application which was originally filed.

The opposition procedure can last up to two and a half years. Once a decision is reached, either party can then appeal against that decision. Such appeals can take up to four years to be decided. They are heard by an Appeal Board within the EPO, selected to hear the specific case. Questions may be referred for resolution to the Enlarged Board of Appeal. The decision of the Appeal Board is final although the validity of granted patents can be challenged through national courts in infringement disputes.¹⁷

US

2.18 In the US, patents can be challenged through litigation, or by a request for 're-examination'. Re-examination can occur at any point during the life of a patent. To succeed, a request must demonstrate some undisclosed 'new' and relevant piece of prior art (that is, any previously used or published technology). Many requests for re-examination are made by the owners of the patent in question themselves. Unlike the EPO procedure for challenging patents, re-examination is not an adversarial process in which both sides can present evidence; it is a formal Patent Office review of the claims of an existing patent to determine whether newly cited prior art affects the validity of the claims. It has been estimated that almost 7% of EPO patents result in opposition proceedings, compared to 0.3% of US patents that result in re-examination.¹⁸ Of these challenges, a minority are successful, and fewer are successful in the US than in Europe. In the biotechnology and pharmaceutical fields, challenges often result in amendment rather than revocation.

¹⁷ If a patent that has been granted is infringed, the owners of patents must seek redress through the various national courts, who also have jurisdiction to revoke a patent, even one that has survived opposition in the EPO.

¹⁸ Merges RP. As many as six impossible patents before breakfast: property rights for business systems and patent system reform. *Berkeley Technology Law Journal* 1999;14:577-615.

- 2.19 Challenging patents, either through the patent offices or through the courts if infringement is claimed, tends to be time-consuming and expensive. At the EPO, the opposition procedure can last for a number of years. Oppositions are normally dealt with in chronological order, but if a patent holder says he wishes to sue for infringement in a national court, priority may be given. Appeals to the Technical Board of Appeals may then take a further two to four years or so.¹⁹ The total costs have been estimated at between £10,000 and £15,000 for each party.²⁰ The cost of patent litigation in Europe is estimated at between £30,000 and £300,000 per case although this may be conservative.²¹ In the US, the filing costs for re-examination of a patent are estimated at between \$10,000 and \$100,000.²² The cost of litigation is estimated at between \$1 and \$3 million per case.²³
- 2.20 We note that in most countries, patent litigation is very expensive and slow. Although the EPO's opposition system for challenging patents in Europe is less costly than litigation in the US, it may be several years before a decision is reached. This is so even though it is likely that a number of patents, though granted, would not be valid if challenged in court. We note that patent offices are working to improve the efficiency of the various methods for challenging patents and welcome such efforts.

¹⁹ However, applications to accelerate the opposition procedure are often effective. There is a widely held view that the delays experienced during the opposition procedures are frequently tactical on the part of the parties involved.

²⁰ Graham JH, Hall BH, Harhoff D, Mowery D. Post-Issue patent 'quality control': a comparative study of US patent re-examinations and European patent oppositions. 9 Feb 2002. http://www7.nationalacademies.org/step/Hall_et_al_paper.pdf (13 May 2002).

²¹ Ibid.

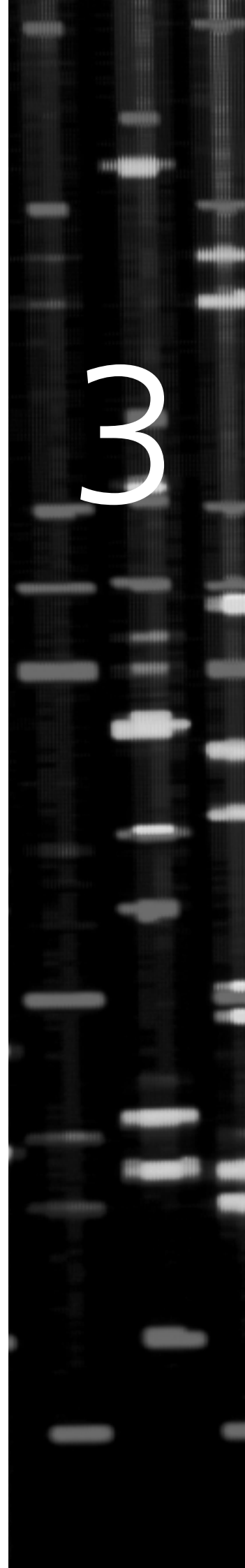
²² Ibid.

²³ Barton J. Reforming the patent system. *Science* 2002;287:1933-4.

Chapter

3

Patenting DNA



Patenting DNA

3.1 In Chapter 2, we accepted that, in general, the application of the patent system in the field of biotechnology and biomedicine is justifiable as a way of striking a reasonable balance between the rights of inventors and the public interest. In this chapter we address the special questions which arise regarding patents that assert rights over DNA sequences. Such patents raise a number of ethical concerns, which can be divided into three types of argument, namely that:

- i) patents that assert rights over DNA sequences, in particular human DNA sequences, should not be allowed by virtue of the special status or nature of DNA;
- ii) patents that assert rights over DNA sequences should not be allowed because they do not meet the legal criteria for patenting;
- iii) patents that assert rights over DNA sequences should not be allowed by virtue of the possible deleterious consequences for healthcare and research related to healthcare.

3.2 We consider the first two of these arguments in this chapter. In Chapter 4, we address the third argument by introducing a number of case studies to illustrate the possible deleterious effects of allowing patents with claims to DNA sequences. In Chapter 5, we consider, in the light of the preceding discussions, whether the current system for granting patents ought to be modified.

The special status of DNA

Genes as our common heritage

3.3 One argument about the special status of DNA focuses specifically on the proposition that human DNA has a special nature, compared to the DNA of other organisms. Many people undoubtedly feel uncomfortable with the fact that genes and their mutations can be claimed for commercial gain. It is argued that the human genome is unique and distinctive, so it should be treated differently from others such as the genomes of mice or maize, for example.

3.4 This view has been expressed by various organisations, including the Council of Europe's Committee on Legal Affairs and Human Rights. The Committee called for the member states of the Council of Europe to strive to change the basis of patent law with respect to rights of ownership over human tissue and genes 'into law pertaining to the common heritage of mankind' in international fora such as the WTO. The Parliamentary Assembly of the Council of Europe, in addition, has approved two recommendations addressing biotechnology and IP.¹ Both reflect unease at the concept of patenting living matter and dissatisfaction with the existing patent system with respect to its approach to dealing with genes, particularly human genes.

3.5 The Parliamentary Assembly further proposed that national governments of the Council of Europe's member states should strive for universal acceptance of a new system termed a new 'World Patent Convention', to be established under the auspices of an international institution or organisation. It recommended that the proposed system be founded on a principle of common heritage, which mirrors the language of UNESCO's Universal Declaration

¹ Parliamentary Assembly Recommendation 1425 (1999) and Recommendation 1468 (2000).

on the Human Genome and Human Rights (1997) in referring to the human genome as the 'common heritage of humanity'.

3.6 References to the common heritage of humanity are easy to understand in the context of shared natural resources such as land or oil. The precise nature of the special status of the human genome is harder to elucidate. Nonetheless, it remains the case that many people feel that genetic information in humans warrants special treatment. Some claim that there should be no property rights in genes; others claim that, while there may be property rights relating to genes, such rights should be the subject of shared public ownership rather than being in private hands. We now consider each of these arguments in turn.

The inalienable nature of genes

3.7 There is an important fundamental constraint on individuals' property rights, namely the respect they owe to others as persons entitled to live a life of their own. This implies, among other things, that people may not be owned by others as slaves. It is argued that this inalienable right to self-ownership brings with it an inalienable right to ownership of one's body, including one's genes. Thus it could be argued that no one can own, or have property rights over, another person's genes; and this principle is widely affirmed – as in Article 5 of the *EC Directive 98/44/EC*²:

(1) The human body, at the various stages of its formation and development, and the simple discovery of one of its elements, including the sequence or partial sequence of a gene, cannot constitute patentable inventions.'

The problem with this argument is that patents with claims to DNA sequences do not entail ownership of genes as they occur in our bodies – they relate instead to the isolated versions of such sequences which are held to be patentable. Thus, Article 5 continues:

(2) 'An element isolated from the human body or otherwise produced by means of a technical process, including the sequence or partial sequence of a gene, may constitute a patentable invention, even if the structure of that element is identical to that of a natural element.'

Much of the difficulty of the question of patenting DNA is encapsulated in the problem of understanding how these two principles can be consistently combined. In the present context, what matters is that Article 5(2) is taken to legitimate, for example, patents on diagnostic tests based on genes, which give the owners of patents control over the way in which use is made of knowledge about genes which are common to everyone.³ We consider the possible undesirable consequences of this situation in Chapters 4 and 5.

Genes as public property

3.8 The second argument is that genes, if they are to be the subject of property rights, should be publicly rather than privately owned. The concept of public property or common heritage has applied, in legal and political terms, to such things as the navigable waterways,

² As at June 2002, five Member States of the European Union had fully implemented the Directive: Denmark, Finland, the UK, Greece and Ireland. The provisions made in the Directive have been endorsed into the EPC under a new chapter entitled 'biotechnological inventions'.

³ It should be noted that under most patent systems, an individual could use knowledge about their own particular genes when those genes had been patented by others, without infringing, provided that it was done in private and for purposes which were not commercial. See for example, the UK Patents Act, 1977, Section 60, Meaning of infringement.

shorelines and public parks. As regards these, the public interest is protected through vesting rights of ownership in the state or some international body, or by declaring that they are not amenable to ownership. Some have argued against this approach on the grounds that it leads to waste, mismanagement and a lack of incentive to find and develop resources.⁴ We observed in Chapter 2 that the patent system has been important for the development of new medicines and other advances in healthcare, and has been mediated by a strong commercial pharmaceutical industry. In any case, it must be noted that, in general, the aim of designating resources as public property or common heritage is primarily to ensure freedom of access. This does not necessarily entail that such resources cannot be developed for profit, provided that such development does not prevent access: the central question is whether such access must necessarily be free and unrestricted. Nor does anything in the argument show that the involvement of private interests and profit-making organisations necessarily entails unjustifiable restrictions on access. This may, in practice, turn out to be the case, but it cannot be assumed in advance.

Genes as discoveries

- 3.9 We suggest that this second concern about rights of ownership under the patent system is rooted in a deeper belief that genes are naturally-occurring entities that are there to be discovered, like new species or new planets. They are not invented. In our common usage of the term, a 'discovery' is the acquisition of knowledge of a new but already existing fact about the world. An 'invention', on the other hand, is something that someone creates or develops which did not previously exist. Thus, on the usual interpretation of the words, it seems apparent that the identification of a gene is a discovery, since genes exist in the world, in our bodies.
- 3.10 In Europe and most other countries, patent law explicitly excludes discoveries from qualifying for the grant of a patent. In the US, although the patent statute states that both discoveries and inventions qualify, in practice the law does not permit the patenting of natural phenomena.⁵ However, under the law in Europe and the US, a discovery that has a useful application may merit consideration as qualifying for the grant of a patent if it is part of an invention.
- 3.11 In the present context, however, the important point is that patent offices maintain that the DNA sequences claimed in patents are not natural phenomena. Instead, they say, patents that assert rights over DNA sequences do not relate to genes as they occur naturally, but rather to genes that have been isolated.⁶ That is, although these DNA sequences do in fact match the sequences of our genes, they are only patented in the context of molecules which have been artificially created by cloning and are isolated from the human body. This thesis brings us to the question of the eligibility of DNA sequences for patenting. (Box 3.1 explains how patents can assert rights over DNA sequences).

Eligibility

- 3.12 In discussing whether DNA sequences are eligible for patenting, we begin by summarising the legal framework in the US and Europe with regard to the patenting of DNA, and set out

⁴ See for example Hardin G. The tragedy of the commons. *Science* 1968;162:1243-1248.

⁵ Title 35 U.S.C. § 101 states 'Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.' However, the Supreme Court has held that patent protection is not available for 'laws of nature, natural phenomena, and abstract ideas.' *Diamond v Diehr*, 450 U.S. 175, 185 (1981).

⁶ This is the distinction drawn in the EC Directive quoted in paragraph 3.7 above; note that Article 5(1) refers to an unpatentable *discovery*, whereas Article 5(2) concerns patentable *inventions*.

Box 3.1: **Patents and DNA**

Are there different types of patent?

Patents can be divided into three categories, though these categories are not formally distinguished in the patent system. A *product patent* is a patent on the product itself. The term 'product' normally means a chemical or biological entity, substance or composition (as distinct from a device or electrical circuit). A patent that asserts rights over a product itself covers all uses of that product.¹ A *process patent* is a patent on a method or process. This covers a process, and may also include what is directly produced from the process. If a product is made by another process, not covered by the patent, it does not infringe it. A *use patent* is a patent on the use of the product for a specific purpose; only the specified use is covered.² For example, in relation to a particular pharmaceutical product, a *product* patent would cover the active ingredient, further *product* patents may cover particular formulations, *process* patents would cover making the active ingredient or formulation, and *use* patents would cover the use of the drug for a specific medical indication. An important feature of product patents is that they extend to new uses of the invention that developed subsequently, even if these uses were not anticipated or predicted by the owner of the patent.

What types of patent can include assert property rights over DNA sequences?

Of the three main kinds of patent, product, process and use patents, only product patents can assert rights over DNA sequences themselves. Use patents only extend to the use of the sequence. In practice, use patents may also restrict access to the DNA sequence itself (see paragraph 5.24).

What kind of products can include DNA sequences as part of their claims?

Various products can include DNA sequences. For example, diagnostic tests that are used to determine whether an individual has a particular genetic variant. Some medicines are developed from proteins, which are produced by a gene. A patent on the medicine may assert rights over the DNA sequence that is needed to generate the protein.

How are patent applications constructed?

Patent applications generally include the following sections:

- i) *Abstract*: A summary of the application;
- ii) *Description*: A description of the invention, such that another person skilled in the art could produce the same invention using this information;
- iii) *Claims*: A definition of the precise scope of the patent, in other words that over which rights are asserted. Some claims are called 'dependent' claims because they are based on another claim. All claims must be clear, complete and supported by the description of the invention. We use the word 'claim' in this technical sense in this Paper.

Why is the scope of a claim important?

The claims contained in a patent are the most important element, since they determine the limits of the monopoly, and therefore dictate what the owner of the patent can prevent others from doing without permission. Claims can be either broad or narrow, and a single patent application will usually contain claims of both sorts. As the names suggest, broad claims contain less detail than narrow claims, and therefore give the owner of the patent protection over a wider range of activities. Broad claims will generate more commercial advantage, but may be more susceptible to attack. When patents are challenged, each claim is assessed independently, so that even if a broad claim is rejected, a narrow claim may be upheld. Patents which contain broad claims are often referred to as broad patents.

continued >>

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In what form do genes or DNA sequences appear in patent claims?

Patent claims may assert rights over DNA in various ways, for example, they may claim one or more of the following:

- the DNA sequence, whether comprising a complete or partial gene
- promoters
- enhancers
- individual exons
- expressed sequences as expressed sequence tags (ESTs) or cDNAs
- whole transcribed genes as cDNAs
- individual mutations known to cause disease
- variation between people not associated with disease (polymorphisms)
- cloning vectors, formed from bacterial DNA, which are used to replicate DNA sequences
- expression vectors, also formed from bacterial DNA, which are used to express proteins in replicated DNA sequences
- isolated host cells transformed with expression vectors, which are cells that have been created to express particular proteins
- amino acid sequences (proteins)
- the use of such proteins as medicines
- antibodies, which are used as markers
- nucleic acid probes, which are fragments of DNA that are used to locate particular parts of DNA sequences
- methods of identifying the existence of a DNA sequence or a mutation or deletion in an individual
- testing kits for detecting genetic mutations
- whole genomes

¹ The term *composition of matter patent* is sometimes used in the United States to refer to a patent on a chemical product. Confusingly, it has been used in relation to both individual substances and true compositions of two or more substances.

² An exception is *first medical use* patents. These are patents on products that are not novel in themselves, but for which no medical use has been previously described. This kind of patent exists only under European patent law. The claims cover manufacture of the known product for all medical uses.

the historical background that has led to the current position. The historical perspective is particularly important because of the rapid development of technology in the life sciences (further details of relevant case law, legislation and regulation are provided in Appendix 2). We then assess briefly the way in which this framework has been applied.

3.13 As we have indicated, substances as they occur in nature and natural phenomena are not eligible for patenting as such. However, processes involving living organisms and versions of natural products which have been isolated have been held eligible for patenting in various countries for many years.⁷ There are many examples of patents granted on isolated natural products and they include Louis Pasteur's 1873 patent on isolated yeast, granted in France and the US, a patent on isolated vitamin B12 held by the pharmaceutical company Merck &

⁷ Brazil is an exception in that its patent law prohibits patents on natural living beings, and biological material including genomes or germplasm of any natural living being whether found in or isolated from, nature. However, genes that have been modified may be eligible for patenting under Brazilian law (Section 1, Article 10 IX of Industrial Property Law No.9279/96).

Co (and upheld in *Merck & Co., Inc. v Olin Mathieson Chem. Corp.*, (1958) 253 F.2d 156, 161, 163), and patents on isolated adrenaline.⁸

- 3.14 In the UK, the 1949 Patents Act was interpreted by the UK Patent Office to mean that the first person to discover and isolate a natural substance could be granted a patent. This was a change from previous policy, which had only allowed substances to be patented if they were created by some particular method of synthesis. In 1988, before the patenting of DNA sequences had become widespread, the EPO, USPTO and Japan Patent Office (JPO) issued a joint statement clarifying the position with regard to isolation:

'Purified natural products are not regarded under any of the three laws as products of nature or discoveries because they do not in fact exist in nature in an isolated form. Rather, they are regarded for patent purposes as biologically active substances or chemical compounds and eligible for patenting on the same basis as other chemical compounds.'⁹

On this basis, isolated genes are deemed to be eligible for patenting despite their origin as products of nature.

- 3.15 As well as isolated natural products, living organisms and processes which involve living organisms can also be eligible for patenting. When plants and animals are naturally-occurring species, 'wild' flowers and animals as we commonly say, there is no question of anyone gaining exclusive patent rights over them. In fact, many of the plants and animals that we encounter have, however, been domesticated by breeding and hybridisation. There is a long tradition of providing incentives to plant breeders through a regime of rights to IP.¹⁰ This reflects the long-standing and widespread acceptance that the work of plant breeders merits encouragement through such a regime.
- 3.16 Perhaps the most well-known example of a living organism which was granted a patent is the genetically engineered bacterium that was the subject of litigation in the US, *Diamond v Chakrabarty* (1980). By a 5-4 decision, the Supreme Court allowed the grant of the patent to stand, US Chief Justice Burger famously remarking that in principle 'anything under the sun that is made by man is eligible for patenting.'¹¹ Other living organisms that have been patented include yeasts, viruses, and cell lines.
- 3.17 European patent law relating to naturally-occurring phenomena and living organisms has evolved along similar lines (see Appendix 2). The *1998 EC Directive on the Legal Protection of Biotechnological Inventions (98/44/EC)* states in Article 3 that:

⁸ Louis Pasteur's patent was US Patent no. 141,072. Merck and Co's patent for vitamin B12 was issued in 1951 claiming a method of producing the pure vitamin crystal. A US court ruled that until the inventors had made vitamin B12 available to the world it did not exist, although the substance was well known to chemists in crude extracts. Jockichi Takamine obtained patents in the US, the UK and Japan for adrenaline (epinephrine) purified from gland tissue. These patents were also challenged but it was ruled that 'for every practical purpose [Takamine had produced] a new thing commercially and therapeutically.' *Parke-Davis & Co. v H. K. Mulford Co.*, 189 F. 95, 103 (S.D.N.Y. 1911) (<http://pubs.acs.org/subscribe/journals/mdd/v04/i12/html/12timeline.html> (13 May 2002)).

⁹ Quoted in Crespi RS. Patents on genes: can the issues be clarified? *Bio-Science Law Review* 1999/2000;3(5):199-204.

¹⁰ In Europe, there are rules for protecting rights over registered plant varieties governed by the 1961 Union for the Protection of New Varieties of Plants (UPOV) Convention. The UPOV system is distinct from the patent system: in Europe, plant varieties created by biological techniques ('breeding') are excluded from patent protection and must be protected under the UPOV rules.

¹¹ In allowing the patent to be granted, Chief Justice Burger, delivering the opinion of the court, stated: 'the patentee [Chakrabarty] has produced a new bacterium with markedly different characteristics from any found in nature and one having the potential for significant utility. His discovery is not nature's handiwork, but his own; accordingly it is patentable subject matter under §101'.

- 'for the purposes of this Directive, inventions which are new, which involve an inventive step and which are susceptible of industrial application shall be patentable even if they concern a product consisting of or containing biological material or a process by means of which biological material is produced, processed or used.
- biological material which is isolated from its natural environment or produced by means of a technical process may be the subject of an invention even if it previously occurred in nature.'

3.18 As we noted in paragraph 3.7, Article 5 of the EC Directive states that an element isolated from the human body or produced through a technical process, including the sequence or partial sequence of a gene, may be patented even where that element's structure is identical to that of a natural element. It can therefore be seen that in both the US and Europe, DNA sequences are regarded by the law, in principle, as being eligible for patenting once they have been isolated from their natural environment. However to be granted a patent, they must meet the legal criteria of being *novel*, *inventive* and having *utility* or being capable of industrial application. The question of whether DNA sequences are eligible for patenting is distinct from the question of whether they meet these legal criteria. In the next section we describe how these criteria are applied with respect to DNA. Before doing so, however, we reflect on the legal reasoning which has led to the practice of regarding DNA sequences as eligible for patenting.

3.19 One common criticism of the thesis that DNA sequences are eligible for patenting is that it fails to take account of the fact that these sequences carry information: they are the body's way of carrying information as to how proteins are to be constructed. But this kind of information, it will be said, cannot properly be patented. It may be discovered and stored on a database which carries a charge for access; but it is simply not eligible for patenting.

3.20 In considering this criticism, it is essential to distinguish two different types of information: (i) information of the kind scientists discover about a natural phenomenon; (ii) a phenomenon, natural or artificial, which is itself essentially information, in the sense that it is a code which is used to control complex activities. Let us call information in the first sense 'scientific knowledge' and, in the second sense, 'genetic information' (there are of course other types of information of this kind, but it is genetic information that is relevant here). As we have seen, scientific knowledge concerning a natural phenomenon is not eligible for patenting, since it is a mere 'discovery'. It follows from this that scientific knowledge about genetic information which is encoded in some naturally-occurring phenomenon is not eligible for patenting as such. But it does not follow that an artificial phenomenon that does not occur naturally (such as a molecule that has been isolated and cloned) that encodes genetic information may not be eligible. This distinction may appear a fine one; but the underlying point is crucial to an understanding of the evolution of the patent system.

3.21 Patent offices take the view that extracting the genetic information encoded by a DNA sequence is not just a matter of gaining scientific knowledge about a natural phenomenon: it involves the use of cloning techniques to create an artificial molecule in such a way that it includes much the same genetic information as is to be found in the natural phenomenon. And what is held to be important here is that the scientific knowledge concerning the genetic information has been discovered through the creation of the artificial molecule. That is to say, without isolating and cloning a gene, it is not possible to identify the

sequence of bases of which it is comprised. Hence, patent offices have concluded, the genetic information is essentially part of an 'invention', a molecule which is human handiwork, and can be patented as such.

- 3.22 The assumption in this defence of the eligibility of artificial DNA sequences, that the isolation and cloning involved does produce genuinely new molecules of a kind which do not occur naturally, can be questioned. Furthermore, the fact that genes are essentially just genetic information makes the issue of patenting them very different from that involved in the isolation of other chemical compounds. But the procedures involved in the early days of cloning genes were certainly inventive and arduous. For this reason, patents awarded in those early days need not now be called into question.
- 3.23 The early days of pioneering experiments using positional cloning techniques are now history, and many DNA sequences which were produced by a combination of computational and cloning techniques have since been the subject of patent claims. Even if it can be convincingly argued that the DNA sequences were eligible for patenting, these patents should be examined in the light of the criteria for inventiveness and utility. We discuss these legal criteria below, and argue that they need to be much more stringently applied than has been the case (paragraphs 3.29 – 3.37). In Chapter 5, we consider further their application to various ways in which DNA sequences can be the subject of property rights asserted in patents.
- 3.24 The defence of the eligibility for patenting of DNA sequences described above (paragraphs 3.20 – 3.21) seems to us even more doubtful as a result of the increasing availability of the sequence of the human genome. Now, it may no longer be necessary to use cloning techniques to identify the DNA sequences of genes; instead they will be identified from computer databases, the cloning and sequencing having been completed previously by other scientists and placed in the public domain. When this method is used, there would seem to be no good reason for holding that a DNA sequence thereby identified is eligible for patenting, even if it were to be subsequently cloned. For, in such a case, the scientific knowledge about the DNA sequence would not be dependent upon the construction and analysis of an artificial molecule. This state of affairs, whereby patent protection may no longer be appropriate for a particular invention, despite it having been readily granted at a time when a technology was at an early stage of development, is a common occurrence in patenting (we say more about this in paragraph 3.31 where we discuss the implications of advances in techniques for isolating genes in relation to the patent system's requirement of inventiveness).
- 3.25 As computational techniques replace cloning as the main route to identifying genes, the issue of the eligibility for patenting of DNA sequences needs to be reopened. The fact that DNA sequences obtained by cloning have in the past been regarded as eligible for patenting does not imply that they should continue to be eligible for patenting when they can be identified from databases constructed by others.
- 3.26 As we observed above (paragraph 3.18), the fact that something is eligible for patenting does not imply that it should receive a patent. It must also satisfy the further requirements of novelty, inventiveness and utility. So, we now discuss the way in which these criteria are applied to patents that assert rights over DNA sequences.

DNA and the legal criteria for patenting

Novelty

- 3.27 To fulfil the requirement of novelty, an invention must not have been previously disclosed to the public.¹² But if a gene or protein is present in nature, can it be said not to be available to the public? Individual genes in their natural state are not directly accessible and additional work is required to isolate them. Is this enough to allow the conclusion that the isolation of a gene is actually deserving of recognition in the form of patent protection?
- 3.28 Lawyers have argued successfully that isolating a gene from its natural environment is sufficient to show that a novel product has been created. The inventor's isolation of a gene separates it from other molecules that are naturally associated with it and allows biochemical characterisation in the form of description of the sequence of the bases.¹³ As we have said, a patent involving an isolated gene does not extend to the gene as it occurs naturally, but only its isolated form. However, even if it meets the criterion of novelty, isolating a gene will be only the first step in meeting the legal criteria for eligibility for patenting. Unless the inventor can also demonstrate an inventive step and a useful application of the isolated gene, a patent will not, or should not, be granted.

Inventiveness

- 3.29 The requirement for inventiveness means that applicants must be able to demonstrate that, when compared with what is already known, the claimed invention would not be obvious to 'the skilled person'; an ordinary worker with a good knowledge and experience of the subject. The parallel requirement in US law is that of non-obviousness. It is generally the case that the more human intervention needed to produce a product, the greater the chances of it being eligible for patenting. There has been considerable debate about whether isolated DNA sequences, as they are used in diagnostic tests, medicines or as research tools, are inventive and non-obvious to the skilled worker.
- 3.30 Many have argued that technological advances in DNA sequencing now mean that the process of isolating a gene can no longer be regarded as inventive, as it is a routine and industrialised process even if the resulting sequence codes for a novel product. Prior to the impact of the large scale DNA sequencing programmes, genes were identified by procedures such as positional cloning and the use of protein sequences to derive nucleic acid sequences.¹⁴ These are time-consuming and labour-intensive techniques, the early application of which was viewed as inventive. The isolation and identification of a novel DNA sequence together with a use, either disclosed or predicted, was the subject of many patent applications.
- 3.31 Since the early 1990s, methods such as the application of *in silico* techniques have been developed. As we have seen, now that the DNA sequence of the human genome is accessible from a personal computer, a researcher can match an unknown human DNA sequence to a homologous, or similar, gene sequence in an animal genome where the function may already be known. The researcher can then file a patent application on the human sequence, based on proposed similarity of function in the context of, for example,

¹² That is, it must not have been disclosed in the prior art (35 U.S.C. 102). Also Article 54 (EPC).

¹³ USPTO Utility Examination Guidelines (Fed. Reg. 66: 1093, 5 Jan 2001); the EC Directive 98/44/EC Article 5(2) (See paragraph 3.7).

¹⁴ Positional cloning is the cloning of a gene based simply on knowing its approximate chromosomal position in the genome without any idea of the function of the gene.

a diagnostic or therapeutic use. These steps can be achieved in the absence of any laboratory work. However, other techniques used for the isolation of disease genes, such as linkage and association studies, continue to require significant effort on the part of researchers.¹⁵ This point reinforces that made earlier in connection with the issue of eligibility (paragraphs 3.22 – 3.25), but it is worth considering separately how these changes in the methods of identifying genes affect the claim that isolated DNA sequences meet the criterion of inventiveness.

3.32 At the EPO, the assessment of inventiveness relates to whether isolating a gene is something that would have been obvious to a person skilled in the art, with regard to the prevailing art at the time, irrespective of whether the sequence itself was structurally obvious or not. The EPO has recently stated that the isolation of DNA sequences that have a structure closely related to existing sequences in which the function is known, is not inventive.¹⁶ The *in silico* approach to identifying DNA sequences is therefore unlikely to provide the grounds for eligibility for patenting in Europe.

3.33 But there are important differences between the US and European approach to assessing inventiveness in respect of claims to DNA sequences. According to the USPTO, non-obviousness does not depend on the amount of work required to characterise the DNA sequence.¹⁷ Rather, it depends on whether a gene having a particular DNA sequence claimed as part of a patent would have been obvious to others at the time. That is, the question is asked: would the sequence of base pairs in the section of DNA have been obvious before the gene was isolated? As it will generally be difficult to predict a given sequence without the isolated gene, the US patent law allows a low threshold on the requirement of inventiveness in the case of patents relating to genes. Moreover, the existence of a general method of isolation of gene sequences is considered to be essentially irrelevant.¹⁸ The USPTO's view, therefore, is that establishing the nature and function of a DNA sequence by electronic means, though a trivial process, does not exclude the granting of a patent on the grounds of non-obviousness.¹⁹

3.34 **We take the view that, on this matter, the test affirmed by the EPO is appropriate.** The test for non-obviousness used by the USPTO means that the outcome of any complex procedure which could not have been predicted in advance, however familiar the procedure, will be judged inventive. While there is a sense in which such a result is 'non-obvious', that is not the sense relevant to questions as to whether a patent should be granted. For example, multiplying two ten-digit numbers will generate an answer that would not be known in advance, but it is nonetheless an obvious result.

¹⁵ In research which aims to identify a gene or a number of genes involved in a particular disease, the approach that is often followed involves linkage or association studies of affected families, which attempt to locate a region of the relevant chromosome that may contain the gene or genes in question. Once this has been achieved, it is then a matter of searching the region on the sequenced genome for causative variation in candidate genes. In its simplest form, an association study compares the frequency of a particular genetic variant in a group of people affected by a certain condition with a matched set of controls (a similar group of people not affected by the condition).

¹⁶ In the Report of Trilateral Project B3b from the European, Japanese and US Patent Offices (http://www.european-patent-office.org/tws/report/report_start_page.htm (13 May 2002)), Nov 2001, Annex 2 p.43, the EPO states that: '*Prima facie*, the routine provision of further sequences having the same general function as the known prior art sequences of closely related structure is not inventive. The structural non-obviousness is not a reason to accept an inventive step; sequences as well as all other chemical compounds should solve a technical problem in a non-obvious manner to be recognised as inventive.'

¹⁷ 35 U.S.C 103 (a) 'Patentability shall not be negated by the manner in which the invention was made'.

¹⁸ *In re Deuel*, 51 F.3d 1552, 1559, 34 USPQ2d, 1210, 1215 (Fed. Cir.1995). See Appendix 2 for further details of this case.

¹⁹ *In re Deuel* is not expected to be followed by the EPO.

Usefulness

3.35 The third criterion that an invention must meet to be eligible for patent protection is that it must be useful. In Europe, this requirement is termed 'capable of industrial application'.²⁰ In the US, the analogous term is that of 'utility'.²¹ It is generally assumed that industrial application is simply the European equivalent of utility.²² For ease of reference in this paper we use 'utility' to refer to both the US and the European criteria.²³ The scope of the US criterion has recently been revised in the new Utility Examination Guidelines of the USPTO, issued on 5 January 2001. These now require an invention to show a 'specific and substantial and credible utility'.²⁴ The term credible is interpreted here as meaning that the usefulness claimed for the invention must be theoretically possible, even though it may not have been demonstrated in the claims. There has been considerable debate over whether DNA sequences in various forms can fulfil the criterion of utility. Since the development of large-scale DNA sequencing techniques over the past ten years, more DNA sequences have become available without a concomitant understanding of their function. As a result, many patent applications have been filed on genes or parts of genes without the demonstration of a 'credible utility'. Such patent applications, involving fragments of DNA, including expressed sequence tags (ESTs) and single nucleotide polymorphisms (SNPs), whose functions are unclear, have been controversial.

3.36 **While we welcome the new USPTO guidelines, we take the view that where 'credibility' means no more than 'theoretical possibility' (i.e. where something is credible simply where it is not incredible) the threshold for utility is still set too low.** The current state of genetics and biochemistry does not make it difficult to suggest functions for DNA sequences that are 'theoretically possible', in the sense that they are not ruled out by what is already known; but this should not suffice for the award of a patent. Instead, what is required is some evidence that the DNA sequence actually has the claimed 'specific' utility and that the claimed utility is truly 'substantial'. Furthermore, the utility in question should be more than a biological function such as encoding a receptor. Even if the biological function ascribed is correct, it is only a description of a fact of nature, and not a practical utility in the usual sense applied to an invented product.

3.37 Even if a credible utility is stated in a patent, if further novel and non-obvious uses for a DNA sequence are found, patent law provides that a product patent on the sequence will extend to cover the new uses, despite their not being specified in the original patent. Thus, an inventor who applies for a patent to cover the new use will have to obtain a licence from the original patent owner if he wishes to exploit his invention. In other words, the

²⁰ Article 52 (1) of the EPC states that European patents shall be granted for any inventions which are susceptible of industrial application, which are new and which involve an inventive step. Article 57 of the EPC states that an invention shall be considered as susceptible of industrial application if it can be made or used in any kind of industry, including agriculture.

²¹ In the US the utility requirement is covered by Title 35 U.S.C. 101: Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

²² The language of Article 57 of the EPC and its national counterparts (see footnote 21 above) is literally broader in its definition of usefulness, because it refers to inventions which can be not only used, but also made, in industry. However, in practice, this is narrowly construed, so that the two criteria are equivalent. This was confirmed in a recent judgment by the English Court of Appeal (*Chiron v Murex* [1996] FSR 153, [1996] RPC 535).

²³ There is a point to be made about the relationship between inventiveness and utility. The EPO's criterion for inventiveness, namely something that solves a technical problem, necessarily implies a degree of utility. It has been suggested that the issue addressed by utility in the US is addressed in Europe partly through the criterion of industrial applicability and partly through that of inventiveness.

²⁴ USPTO Utility Examination Guidelines Fed. Reg. 66: 1092, 5 Jan 2001.

exploitation of his patent becomes dependent on the original patent.²⁵ This situation is well established in the patenting of chemical compounds such as medicines. However, it has been suggested that such dependency on the exploitation of new uses of the first patent is difficult to avoid in the case of patents with claims to DNA sequences because it is difficult to 'invent around' a naturally-occurring gene sequence. (We consider the question of inventing around in paragraph 5.12.)

Types of DNA sequence

Background

3.38 Patent law deals with different types of claims to DNA sequences (see Box 3.1). It is now apparent that different patents that relate to the same gene often contain claims which overlap. This situation arises because a gene, which exists inside a cell as sections of DNA, is an entire functional unit, encompassing coding DNA sequences, called exons, control regions consisting of non-coding regulatory DNA sequences, and functionless 'introns'. A gene with, for example, 15 exons could well have a separate patent claim on each of several of these exons, which would have been discovered as expressed gene fragments (see paragraph 3.40), another claim on the complete expressed sequence discovered by screening a library of expressed gene clones, a separate claim on a promoter sequence and perhaps another on a distant locus control region found to influence the expression of the gene. Each of a number of mutations found to cause disease in different individuals, or different populations, may be the subject of a separate patent claim. Until we have a full appreciation of the assembled human genome, it will not become apparent to what extent existing patent that assert rights over DNA sequence overlap each other.

Full-length DNA sequences

3.39 The most common patent applications that assert rights over DNA sequences have been for the use of genes in the diagnosis of gene-related disorders or for use in medicines, either indirectly by coding for a therapeutic protein, tangentially as a potential target in drug research, or directly, by the intended use of the gene in gene therapy. Other common applications relate to research where the DNA sequence may be used to screen for new medicines, or as markers for disease. Many patent applications claim multiple uses of a gene. Various uses of patented gene sequences are illustrated in the case studies in Chapter 4.

Expressed Sequence Tags (ESTs)

3.40 Researchers have made extensive use of partial DNA sequences or ESTs which are easily identified when particular genes are being expressed. In the 1990s, ESTs were widely used as a shortcut to identifying genes and as a means of studying gene expression. Several companies and other organisations filed patent applications claiming EST sequences in the hope that they would manage to secure exclusive rights to the whole genes at a later stage. As the biological function of these partial gene sequences was usually unknown, they were usually claimed as research tools which could be used for the identification of genes. Although the USPTO rejected a patent application for human ESTs with no known biological function in 1991, large numbers of patent applications on ESTs have since been filed. The prospect of researchers being rewarded for the routine isolation of parts of a gene in which the biological function is unknown has attracted a great deal of criticism. Many have taken the view that ESTs should not qualify for patent protection because their production is neither inventive nor useful.

²⁵ A dependent patent is one whose exploitation would encroach upon the exploitation of an earlier patent. A dependent patent becomes independent with the expiration of an earlier patent.

- 3.41 ESTs are not in principle excluded from eligibility for patenting by the patent system. However, the USPTO's new Utility Guidelines state that the subject of a patent must have a well-established utility that must be readily apparent to one skilled in the art.²⁶ The 1998 EC Directive explicitly excludes the patenting of partial or entire gene sequences where the function of the DNA sequence is unknown. Very few patents on ESTs have been granted (although it is hard to obtain accurate figures because, in patent claims, EST is a term that defines how the fragment of DNA was obtained and not what it is). It appears most unlikely that further patents on ESTs will be granted because they would not meet the utility requirement.²⁷
- 3.42 Patents on ESTs may extend to subsequent patent applications involving full-length DNA sequences in which the biological function is known. The claims in these patents have tended to use what is called 'comprising' language meaning that a patent with a claim to a sequence 'comprising' or containing an identified EST sequence would be infringed by a patent application that claimed the full-length gene that included the EST. It has been suggested that a proliferation of patents on individual ESTs held by different owners raises the prospect of costly future transactions to collect licences together before a company could acquire the rights to develop future commercial products.²⁸ This could lead to the situation where a pharmaceutical company seeking to use a protein would infringe any patents held by others that had identified ESTs present in the DNA sequence (see paragraph 5.38).

Single Nucleotide Polymorphisms (SNPs)

- 3.43 Similar concerns have been expressed over the prospect of patenting SNPs which occur in the human genome. SNPs are single base pair differences occurring at a frequency of about 1 in every 1000 nucleotides when the genome sequences of many individuals are compared. SNPs will be valuable, amongst other things, for studying the genetics of disease and the genetic basis for the response of patients to medicines. The association of SNPs with specific genes implicated in susceptibility to diseases or response to medicines will be of use primarily for the identification of new targets for drugs. Given that SNPs are tiny, naturally occurring changes in DNA that are used as markers, they have been widely thought of as scientific knowledge that should be freely available. A consortium of ten pharmaceutical companies and the UK Wellcome Trust has been established to support the creation of a SNP map of the human genome. This consortium (TSC) will accelerate the search for genes associated with disease by making the map available to all researchers. The aim is to prevent research into substantial areas of the human genome from being impeded or hindered through the lodging of claims for patents in relation to SNPs.²⁹ The initiative also aims to avoid duplication of effort. However, it has been suggested that there will still be patent applications, at least in the US, on the information which links SNPs to particular genes (the 'association') and which would seek to protect the use of

²⁶ USPTO Utility Examination Guidelines Fed. Reg. 66: 1092, 5 Jan 2001. The USPTO has indicated that patents with claims to ESTs could be granted in the context of inventions using partial DNA sequences as molecular markers or probes to identify specific sequences.

²⁷ The company Incyte was granted a patent in 1999 for human kinase homologues based on 12 EST sequences for use as molecular probes (US patent US 5817479). This patent was granted on the basis of the predicted function of the genes from which the ESTs were derived. The USPTO could therefore argue that the patent granted did not cover ESTs with 'no known genetic function'. The Incyte patent is widely regarded as an aberration. No patents on ESTs have been challenged in the courts.

²⁸ Heller M and Eisenberg R. Can patents deter innovation? The anticommons in biomedical research. *Science* 1998;280:698-701.

²⁹ Masood E. Consortium plans free SNP map of human genome. *Nature* 1999; 398:545-546. For further information see website for The SNP Consortium: <http://snp.cshl.org> (20 June 2002).

specific genetic information to infer characteristics about the organism.³⁰ Such a development is likely to be premature in that it is likely to restrict the use of genetic information that has wide applications.

Exceptions to eligibility for patenting

3.44 Applications for patents which involve claims to DNA sequences can be granted, as has been seen, provided they meet the legal criteria for patenting. However, there are some inventions that meet the necessary legal criteria for patentability which are excluded from patenting under various international agreements:

- The *TRIPS Agreement (Trade-Related Aspects of Intellectual Property Rights)* (1994) of the World Trade Organisation (WTO) addresses the issue of the eligibility of subject matter for patenting in Article 27. It permits the exclusion of inventions which threaten the '*ordre public*' or morality. Inventions which deleteriously affect human, animal or plant life or health or which may seriously prejudice the environment may also be excluded. However, the TRIPS agreement does not address directly the question of patenting DNA sequences.
- The *European Directive on the legal protection of biotechnological inventions (Directive 98/44/EC)*³¹, by Article 6, prohibits patents on processes for cloning humans, the modification of the human germ line, and the use of embryos for industrial or commercial purposes.³² In line with the TRIPS agreement, the Directive notes that inventions should be considered unpatentable when the commercial exploitation of them would be contrary to '*ordre public*' or morality.
- The EPC, in Article 53, states that patents shall not be granted in respect of:
 - '(a) inventions the commercial exploitation of which would be contrary to '*ordre public*' or morality, provided that the exploitation shall not be deemed to be so merely because it is prohibited by law or regulation in some or all of the Contracting States;
 - (b) plant or animal varieties or essentially biological processes for the production of plants or animals; this provision does not apply to microbiological processes or the products thereof.³³

3.45 How are phrases such as '*ordre public*' and 'contrary to morality' to be understood? The EPO has defined the concept of '*ordre public*' as covering the protection of public security and the physical integrity of individuals as part of society, and the protection of the environment. The case law of the EPO Board of Appeal states that the concept of morality is:

'...related to the belief that some behaviour [is] right and acceptable whereas other behaviour [is] wrong, this belief being founded on the totality of the accepted norms which [are] deeply rooted in a particular culture. For the purposes of the EPC, the culture in question [is] defined as the culture inherent in European society and civilisation. Accordingly, inventions the exploitation of which [is] not in conformity with the

³⁰ See Barton J. Patents, Genomics, Research and Diagnostics. Forthcoming under the auspices of the Association of American Colleges.

³¹ Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions.

³² Provisions made in the TRIPS agreement and other specified international agreements take precedence over those set out in the Directive, as regards the obligations of members of the EU.

³³ In November 2000, the existing prohibition on patents for methods of treatment such as surgery, therapy or diagnosis, was altered, so that rather than being inventions not susceptible of industrial application, such inventions become classified as simply not patentable, like those in Article 53(a).

conventionally accepted standards of conduct pertaining to this culture [are] to be excluded from patentability as being contrary to morality.³⁴

The difficulty of defining a shared European culture should not be under-estimated. The ongoing debate about the ethical propriety of research on stem cells derived from human embryos provide a vivid example of the lack of a common set of 'accepted standards of conduct' on such questions.

- 3.46 A useful illustration of the application of Article 53 is the opposition in Europe to the grant of a patent for the 'Harvard oncomouse', a strain of mouse developed in the laboratory which has a predisposition to developing tumours. The USPTO granted a patent on the mouse in 1998.³⁵ A patent application was filed at the EPO in 1985 and was first refused by the Examining Division on the grounds that animals were not patentable under Article 53(b) of the EPC.³⁶ The applicant filed an appeal which was successful, and in 1992 the patent was granted. Subsequently, 17 Oppositions against this patent were filed, most concerning animal welfare. The Examining Division was thus required to consider whether Article 53(a) applied. To do this, it engaged in what was an essentially consequentialist analysis, weighing the suffering of the animal and the possible environmental risks against the potential benefits to humanity. The EPO concluded that the patent should stand. It noted that, if restrictions on particular technologies were called for, this should be dealt with by legislation, not through the patent system. It also stated that three different interests had to be balanced: 'a basic interest of mankind to remedy widespread and dangerous diseases', the protection of the environment 'against the uncontrolled dissemination of unwanted genes', and the avoidance of cruelty to animals.³⁷
- 3.47 Applying this approach, the Examining Division found that the invention was unquestionably of value in the development of treatments for cancer. It also noted that the use of the oncomouse would reduce the number of animals required in research, that animal models of cancer were generally considered indispensable, and that the risk to the environment was small. Finally, it stressed that these considerations only applied to the case in question and that other transgenic animals might not be eligible for patenting under the morality clause. In general, the EPO takes the view that each case must be assessed individually to ascertain whether it falls under this clause.
- 3.48 We note that the scrutiny of patent applications by reference to their being contrary to morality or '*ordre public*' requires expertise in areas that may not be represented in patent offices. These areas include moral philosophy, environmental ethics and public policy. For this reason, groups such as the European Group on Ethics, have called for independent ethical evaluation of patent applications in controversial areas, such as stem cell technology.³⁸ **We recommend that the European Patent Office (EPO) should consider producing further guidance which clarifies the principles set out in Article 53(a) of**

³⁴ Case law of the board of appeals. EPO.org. http://www.european-patent-office.org/legal/case_law/e/l_B_2.htm (13 May 2002).

³⁵ The USPTO has subsequently issued numerous patents on transgenic mice as models of specific pathologies, including a mouse that develops an enlarged prostate gland; transgenic mice depleted in mature T-cells; a virus-resistant mouse that produces beta-interferon, and a mouse that displays the amyloid deposits typical of Alzheimers' Disease. See Woessner W. Patenting Transgenic Animals. *J of the Patent and Trademark Office Society* 2001;83:830.

³⁶ See paragraphs 2.18 – 2.21 for an explanation of the system for opposing patents at the EPO.

³⁷ The EPO statement can be found in: Decisions of the Examining and Opposition Divisions. Official Journal of the EPO Oct 1992.

³⁸ The European Group on Ethics in Science and New Technologies. Ethical aspects of patenting inventions involving human stem cells. 7 May 2002. Available at http://europa.eu.int/comm/european_group_ethics/docs/avis16_en.pdf (20 Jun 2002).

the European Patent Convention (EPC) concerning patents that are contrary to morality or *'ordre public'*. We recommend that the EPO seeks general guidance from the European Group on Ethics (EGE).

Summary

- 3.49 In this chapter, we have considered the question of whether DNA sequences should be eligible for patenting. We draw an important distinction between the acquisition of knowledge about the nature and function of a DNA sequence, and the information contained within that sequence. Even though we think that the judgement that isolated DNA sequences are eligible for patenting is based on a questionable extrapolation to the case of genetic information from the case of the isolation of chemical compounds, we accept that a limited number of the early patents granted on that basis need not now be called into question, in view of the inventiveness required to isolate the DNA sequences. Since the early days of the pioneering experiments using positional cloning techniques, patents have been filed on many DNA sequences which were mass-produced by a mixture of computational and cloning techniques. Even if it can be convincingly argued that these sequences were eligible for patenting, the patents should be examined in the light of the criteria for inventiveness and utility. We note that as techniques have advanced, and in particular as the use of computers to identify genes has become more widespread, the eligibility of DNA sequences for patenting should have diminished.
- 3.50 With regard to the legal criteria for assessing patents with claims to DNA sequences, while we accept that the test of novelty can be met, the tests of inventiveness and utility are more problematic. In the case of inventiveness, we hold that as the use of computational databases becomes the standard way of identifying genes, it is difficult to see how the test can be met, despite current US practice. In the case of utility, we argue that the standard of credibility required for a claimed utility needs to be set higher than the mere theoretical possibility of this utility; some positive evidence that the DNA sequence has the claimed utility should be required. Finally, we consider the requirement that patents should satisfy the condition of not being contrary to morality or *'ordre public'*, and suggest that patent offices should seek general ethical guidance, as necessary, from relevant bodies.

Chapter

4

Case studies

Case studies

4.1 The following five case studies have been chosen because they represent a range of patents that assert rights over DNA sequences and that have implications for healthcare. The case studies concern a gene associated with susceptibility to breast cancer called BRCA1, a receptor that is important in HIV/AIDS called the CCR5 receptor, the DNA sequence of the hepatitis C and hepatitis B viruses, and the DNA sequence of a protein from the malarial parasite. We highlight a range of issues raised by each case study, which inform our discussion in Chapter 5.

Case study 1: BRCA1 - susceptibility to breast cancer

4.2 Two genes have so far been discovered which indicate susceptibility to breast cancer, BRCA1 and BRCA2. In this case study we discuss BRCA1, the first such gene to be discovered, which is located on chromosome 17.¹ The gene and its mutations have been part of numerous patent applications by a range of privately and publicly-funded research groups.

4.3 The original discovery of the BRCA1 gene was reported in 1994 by researchers from the University of Utah and the US company Myriad Genetics. In 1995, two patent applications were filed jointly by Myriad Genetics, the University of Utah Research Foundation and the US Secretary of Health, and were subsequently granted.² The applications asserted rights over the normal BRCA1 gene sequence and various mutations, diagnostic tests for detecting mutations in BRCA1, and methods for screening samples taken from tumours. The same year, Myriad Genetics filed an application with the Centre du Recherche du Chul in Canada and the Cancer Institute in Tokyo, Japan, for a patent that claimed a number of mutations in the BRCA1 gene. This patent was awarded in 1997.³

4.4 In 1996, another US patent application was filed by a company called OncorMed for a 'consensus sequence' of the BRCA1 gene. The patent, which was awarded in 1997, asserts rights over a method of identifying individuals with a normal copy of the gene, and of identifying seven mutations in the gene.⁴ In 1998, after claims and counter-claims of infringement, Myriad Genetics acquired the rights to the genetic testing business of OncorMed. In January 2001, Myriad Genetics was granted a European patent that asserted rights over the diagnostic use of the BRCA1 gene (but did not claim the sequence itself).⁵ As a result of this patent, Myriad Genetics has a temporary monopoly on diagnostic testing for BRCA1 in many European countries.

4.5 In the UK, negotiations between the Department of Health and Myriad Genetics are still in progress regarding the provision of services for genetic testing for BRCA1. Laboratories in the NHS continue to conduct tests on the genes and there is no indication that Myriad Genetics has placed any pressure on the NHS to cease testing, despite their patent.

4.6 In October 2001, an opposition procedure was filed jointly by three French organisations against Myriad Genetics' European patent on BRCA1.⁶ Additional oppositions have also been

¹ Only a small proportion of cases of breast cancer are accounted for by mutations in this gene.

² US patent 5,747,282 and US patent 5,710,001.

³ US patent 5,693,473.

⁴ US patent 5,654,155.

⁵ European patent 699754.

⁶ The organisations involved are the Institut Curie, the Assistance Publique-Hôpitaux de Paris and the Institut Gustave-Roussy.

filed by other organisations including the Belgian Society of Human Genetics and the Danish Society for Medical Genetics. The patent is being challenged on the grounds that it is not inventive and that it does not sufficiently describe the inventions over which it asserts property rights.⁷ The opposition is aimed at curtailing any possible deleterious consequences which might stem from sanctioning the monopoly conferred on Myriad Genetics, including possible threats to the development of research and the identification of new tests and diagnostic methods. It has also been argued that the patent will have a serious impact on equitable access to testing. It is suggested that the monopoly is antithetical to an approach to public health that is based on a commitment to the comprehensive care of patients at high-risk.

4.7 The three French joint opposing parties, and the Belgian and Dutch Centres for Human Genetics, the Belgian Ministers of Health, Social Affairs and Scientific Research, and the Dutch Minister of Health, filed oppositions to a second patent of Myriad Genetics in February 2002. This is a European patent granted in 2001 which covers a method for diagnosing susceptibility to breast and ovarian cancer linked to the BRCA1 gene and covers the use of a further 34 specific mutations of the gene in diagnosis.⁸ The patent was challenged on the grounds that it was not inventive, that it lacked industrial applicability and again that it was excessively broad in its reach, covering all possible diagnostic methods. None of the Oppositions has yet been decided upon.

4.8 The potential impact of Myriad Genetics' monopoly on the diagnosis of a susceptibility to breast cancer prompted the government of France to revise its legal framework to facilitate access to diagnostic testing by broadening compulsory licensing schemes or equivalent measures.⁹ Across Europe, the patents have faced mounting opposition from genetics societies. The European Parliament adopted a resolution in October 2001 opposing the patenting of the BRCA1 gene.

Box 4.1: Case study 1 - Issues

- Is it in the public interest that there is only one diagnostic test available for a particular disease?
- Will patents on diagnostic tests prevent other diagnostic tests from being developed and used? Alternatively, will they stimulate further development?
- Will patents such as those that assert rights over BRCA1 inhibit further research, even in the context of other diseases?

⁷ The opposition contends that the protein sequence used for Myriad's first patent application on a diagnostic test is *per se* insufficient for producing a test for susceptibility to breast cancer.

⁸ European patent 705903.

⁹ In Canada, Myriad Genetics has demanded that all screening tests based on the BRCA1 gene mutations on which it holds patents be done through its own laboratories. Publicly-funded laboratories in Ontario, British Columbia, Quebec and Alberta had been using other tests, and the threat of legal action prompted British Columbia to suspend temporarily the funding of predictive tests based on the patented genes. The province continues to provide counselling services for patients who pay for testing themselves. Quebec has begun sending samples to Myriad Genetics for testing. Only Ontario and Alberta, of the provinces that previously offered the tests, continue to fund predictive screening programmes. Ontario decided that the precedent that they would set by agreeing to Myriad Genetics' request was undesirable. So far, Myriad Genetics has not taken further legal action against Ontario, despite being aware of its position. (See Eggerston L. Ontario defies US firm's genetic patent, continues cancer screening. CMAJ 2002;166(4):494).

Case study 2: The CCR5 Receptor – HIV/AIDS

- 4.9 In February 2000, Human Genome Sciences Inc (HGS), a US company, was granted a US patent which asserted rights over the gene that codes for the CCR5 receptor.¹⁰ The CCR5 receptor is the route by which the HIV/AIDS virus enters a cell. When HGS originally isolated the gene for this receptor and filed for the patent in June 1995, its estimate of how it would meet the criterion of utility was that the CCR5 protein product would be a cell-surface receptor. Their patent claims did cover a viral receptor, but at the time, they were unaware of the receptor's role in HIV/AIDS. Instead, the researchers expected to exploit the patent primarily for the development of anti-inflammatory therapies. Subsequently, the role of the CCR5 receptor in HIV/AIDS was revealed by other researchers, six months after HGS filed its patent application. Another researcher, Dr M Parmentier, had isolated the gene some years earlier but only filed a patent application in March 1996 when its biological function had been confirmed. His team and a number of other research groups simultaneously published the finding that CCR5 was indeed a critical site for entry of the HIV virus into the cell. Parmentier's patent has not yet been granted.
- 4.10 HGS has already agreed to several licences for the use of the CCR5 receptor gene in research into new drugs. In one recent example, Praecis Pharmaceuticals was licensed to develop therapies for AIDS, employing the receptor. Future therapeutic interventions will depend on licensing of the HGS patent. At present, it appears that HGS does not plan to prevent academics from undertaking unlicensed research involving CCR5.

Box 4.2: Case study 2 - Issues

- To what extent is it reasonable that an estimate of utility be rewarded?
- Should the established principle that a patent applies even to an unanticipated utility apply in the case of DNA sequences?
- What entitlement should the team which actually identified the role of CCR5 in HIV/AIDS enjoy?
- What would be the impact of patents such as this on research if they were not licensed generously?

Case study 3: Gene-based diagnostic test for hepatitis C

- 4.11 Appropriate tests for hepatitis A and B were developed in the 1970s, but the hepatitis C virus (HCV) was not identified for a further 12 years, despite substantial research programmes. Scientists from Chiron Corporation in the US cloned HCV in 1987 and identified its role in some forms of hepatitis. This was the first time an infectious agent had been identified by molecular cloning techniques alone and was a fundamental breakthrough in research into infectious diseases. As a result of its groundbreaking research, Chiron was granted a broad UK patent on the viral components of HCV and the use of them in diagnostic tests.¹¹ A European patent was subsequently granted and then opposed.¹² The Opposition Division of the EPO broadly upheld the claims, but on appeal, significant amendments to the claims were

¹⁰ US patent 6,025,154.

¹¹ UK patent 2212511.

¹² European patent 0318216.

made. In effect, the claims in the patent were limited to nucleic acid probes and PCR materials for the detection of HCV. The original claims relating to immunoassays and antigens were held to be unsubstantiated in the form granted.

- 4.12 At present, Chiron has been granted in excess of 100 patents related to HCV in over 20 countries. Its tests have been liberally licensed, widely used and have created considerable income for the company. Chiron has successfully defended its broad patents against a number of legal challenges and has enforced its patent rights against companies who have infringed its patents by producing unlicensed tests, or have sought to develop novel medicines or vaccines without a licence.
- 4.13 Although the case of HCV concerns the patenting of viral, rather than human, genes, it raises issues similar to those in the previous case studies. A key question is whether the patent did meet the necessary legal criteria: was the isolation of the viral components clearly inventive? Chiron's achievement was held to have met the legal requirements for patenting, namely novelty, inventiveness and utility. Others have taken the view that their diagnostic test was not sufficiently inventive. In any case there has been concern expressed over the breadth of the patent granted. When Chiron first sued for infringement of the patent relating to diagnostic tests, the defendants counter-claimed that Chiron's patent be revoked. To the extent that the patent explicitly asserted rights over vaccines against HCV, it was held invalid, because the patent did not contain enough instructions on how to make a vaccine (indeed, no vaccines yet exist). However, the company was still left with a patent covering a DNA sequence which is relevant to such a vaccine. Arguably, if others produce a vaccine, it will have to be based on Chiron's work and the sequence patented by them, although it may be possible to produce a so-called 'anti-idiotypic' vaccine which gives rise to an immune response against the patented protein but does not contain it.

Box 4.3: Case study 3 - Issues

- Should groundbreaking research be rewarded with broad patents, for example patents conferring the exclusive use of DNA sequences in diagnostic tests?
- How far should claims in a product patent that cover the use of sequence in one area extend to other uses such as medicines and vaccines?

Case study 4: Hepatitis B

- 4.14 The US company Biogen filed an initial patent application in the UK in 1978. It asserted rights over the development of hepatitis B virus (HBV) antigens using recombinant technology. Biogen subsequently filed a European patent one year later. In 1992, Biogen claimed that another company, Medeva, had infringed its patent by producing a vaccine for hepatitis B called 'Hepagene'. Medeva also used technology based on recombinant DNA techniques but used a different method. Biogen commenced legal proceedings against Medeva. In response, Medeva counter-claimed that Biogen's patent was invalid. The question to be resolved was whether Biogen's original patent justified rights over a monopoly over any recombinant method of making antigens.
- 4.15 In the decision in the House of Lords, Lord Hoffmann held that the claims in Biogen's patent were too broad and that the company did not have a monopoly on all recombinant methods of making antigens. Its breadth was excessive due to the fact that the same results could be produced by different means. In fact, once the DNA in question had been

sequenced, no one would choose to use the route set out in the initial patent. Lord Hoffman said that 'care is needed not to stifle further research and healthy competition by allowing the first person who has found a way of achieving an obviously desirable goal to monopolise every other way of doing so'.¹³ The House of Lords found that since Biogen's invention had been obvious by the time its European patent application had been filed in 1979, the patent was invalid.

Box 4.4: Case study 4 - Issues

- Are there sufficient safeguards to enable the patent system to be corrected where patents that assert property rights over DNA sequences are too broad?

Case Study 5: Malaria – MSP-1 protein

- 4.16 The development of vaccines and medicines for diseases prevalent in the developing world is often subsidised by the public sector because the markets for healthcare products are too poorly developed or too diffuse to attract commercial investment. There have, however, been a number of recent initiatives which have brought publicly-funded and privately-funded organisations together to try and address some of the more urgent health needs of developing countries. The Malaria Vaccine Initiative (MVI) is one such initiative which aims to develop vaccines for malaria. MVI is part of the Programme for Appropriate Technology in Health (PATH), an international charitable organisation, dedicated to improving health in developing countries. PATH has been considering whether to provide support for the development and commercialisation of various candidates for a malaria vaccine.
- 4.17 Some potential vaccines against malaria currently being considered for development and commercial use are likely to rely on a particular antigenic protein produced by the malaria parasite called MSP-1.¹⁴ PATH discovered that the group of different patents which related to MSP-1 was complex, in part because many of the patents were very similar. This is attributable both to the fact that the protein was not well-defined in the early stages of research and the lack of effort shown by patent applicants and to a lesser extent, examiners to more fully appraise themselves of existing patents before filing or granting patents respectively.
- 4.18 In the US, five core patents relating to MSP-1 were identified, with about a dozen other patents relating to 'add-on' technologies, which generally concerned specialised antigens and nucleic acid sequences of potential utility in constructing a vaccine. A further five patents specifically related to the production of MSP-1 vaccines. In general, there was a lack of reference to previous, relevant patents in almost all the MSP-1 patents. Before investing in the development and commercial use of a vaccine based on MSP-1, it was necessary to establish:
- whether there were patents that were pending or granted which asserted rights over the MSP protein and the DNA encoding it, the methods of producing the protein, and its use in malaria vaccines, and;
 - which of these patents were likely to be of most relevance to the commercial use of the vaccine in question.

¹³ *Biogen Inc v Medeva Plc* [1997] RPC 1 House of Lords.

¹⁴ MSP-1 is the merozoite surface protein.

It took considerable time and resources for PATH to negotiate with individual owners of the patents to obtain the necessary agreements to proceed with its research.

Box 4.5: **Case study 5 - Issues**

- Do complex and contradictory patents on research tools serve the public interest if they hinder the development of products related to healthcare?

Chapter

5

Discussion

Discussion

Introduction

- 5.1 The overall aim of the patent system is to promote the public interest and to provide a fair reward to inventors by offering protection to inventors in return for disclosure of their inventions. In Chapter 2, we took the view that in general, the patent system is justified because it provides an important incentive for the development of new products and technologies related to healthcare. In Chapter 3, we saw that the legal framework in most countries has been interpreted to permit the assertion of property rights over DNA sequences, though we raised some doubts about the eligibility of DNA sequences for patenting and about whether they satisfy the legal criteria for patenting. Furthermore, the case studies in Chapter 4 and other examples show that the application of patent law to biological molecules such as DNA has raised a number of ethical and legal issues. In the light of these issues, we now assess further the application of the patent system in relation to DNA sequences and the use of such sequences.
- 5.2 In general, the law has, in our view, tended to be generous in granting patents in relation to DNA sequences. Not only are many of the patents broad in scope, but they have been granted when the criteria for inventiveness and utility were weakly applied. Many of these patents are broad because an inventor who successfully makes a claim in relation to a DNA sequence will, in effect, obtain broad protection on *all* uses of the DNA, and sometimes the proteins which the DNA produces. This is because the patent system provides that in the case of patents directed to novel and inventive DNA and other chemical entities, inventors are entitled to property rights not only over the uses of their invention that they anticipated or predicted, but also over any new uses that are developed. The case studies also reveal that some patent offices have been willing to adopt low thresholds for inventiveness and utility.
- 5.3 Since there are various ways in which rights can be asserted over DNA sequences in patent applications, a generalised consideration of these patents would generate a superficial and unsatisfactory analysis. Although many patents will contain claims to more than one way of using a DNA sequence, we distinguish four applications of DNA sequences in relation to patent claims and consider them separately:
- i) *Diagnostic testing*. The presence of a faulty gene in an individual can be detected by techniques based on knowledge of the structure of the gene. Examples include the gene BRCA1 which is associated with a susceptibility to breast cancer (Chapter 4, case study 1).
 - ii) *Research tools*. Since all genes encode parts of biological pathways and systems, knowledge of their DNA sequence can help in the identification of potential targets for which new drugs can be designed and in the development of new vaccines. The identification of a gene may belong to the broad category of scientific findings which have no immediate commercial use in themselves but which have been dubbed 'research tools' since they can, like any other scientific knowledge, guide the design of future research.¹ Examples include the CCR5 receptor and the MSP-1 antigens (Chapter 4, case studies 2 and 5).

¹ We use the term 'research tools' as defined in the Report of the National Institutes of Health (NIH), Working Group on Research Tools, 1998. In that Report the term is defined thus: 'We use the term "research tool" in its broadest sense to embrace the full range of resources that scientists use in the laboratory, while recognizing that from other perspectives the same resources may be viewed as "end products".' DNA sequences are one such class of resources.

- iii) *Gene therapy*. The aim here is to replace a faulty gene with a normal gene by introducing it into the body. This approach is being pursued in the development of treatments for diseases including cystic fibrosis, various cancers and disorders of the immune system.
- iv) *The production of therapeutic proteins to be used as medicines*. Here, a distinctive therapeutic use has been identified for the protein encoded by the DNA sequence. Examples include Epo and human insulin.

1. Diagnostic testing

Background

- 5.4 The identification of DNA sequences that are significantly implicated in a disease can provide the basis for a diagnostic test. We have already seen that a gene implicated in some forms of breast cancer has been used to develop such a test (Chapter 4, case study 1). The BRCA1 test is protected by product patents (see Box 3.1), which assert rights over the DNA sequences and the proteins they encode, and by use patents, which contain claims to the use of the DNA sequences for diagnosis. As we noted in Chapter 4, there has been considerable opposition to the grant of these patents, primarily because it confers on the owners of patents not only a monopoly on their own diagnostic method, but also the ability to prevent others from competing with them through the development of improvements in the diagnostic methods, using the same DNA sequence. Thus, there are currently no other methods of diagnosing the presence of the breast cancer susceptibility gene BRCA1 that can be used without infringing the patents. The resulting exclusive ownership, and the fact that Myriad Genetics has not licensed others to use its patents widely, have enabled the company to establish an exclusive market for its test in the US.
- 5.5 Over the past ten years, many genetic mutations which cause disease have been identified and used as a basis for clinical diagnosis. Some of these mutations of individual genes, such as those that cause cystic fibrosis and haemochromatosis, have been the subject of patents relating to diagnostic tests. The incidence of diseases in which a single gene is involved is relatively infrequent, although there are exceptions: for example, the blood disorders thalassaemia and sickle cell disease are common in some parts of the world. The genetic basis for the majority of common diseases and disorders appears, in fact, to be more complex. The development of such diseases and disorders is affected by a number of factors (hence the term multifactorial disorders), which may include any number of genes (hence the term polygenic), as well as environmental factors. Consequently, the identification of those genes which are important for the prediction of diseases is necessarily more complicated. Moreover, the strength of the predictions is inevitably weaker as, individually, each gene may have a small effect.
- 5.6 Although doubts exist that such genes will enable reliable predictions to be made of disease, some investment is being put into developing a new generation of diagnostic tests which will aim to alert patients and their doctors to a predisposition to major diseases.² The promise, or at least hope, of the protection provided by the patent system is an important part of the strategy behind the investment. It seems very likely that protection will be sought for the

² The SNP approach is based on the 'common disease-common variant' hypothesis; it is unclear to what extent common diseases will be attributable to common rather than rare variants. Additional difficulties with the SNP diagnosis approach are the low relative risks conferred by most susceptibility alleles, the unknown mechanisms of interaction between independent susceptibility alleles, and the statistical challenges of differentiating the association from the effects of change when testing many (possibly hundreds of thousands). See Zwick ME, Cutler DJ, Chakravarti A. Patterns of genetic variation in Mendelian and complex traits. *Ann Rev Genomics Hum Genet* 2000;1:387-407.

DNA sequences of relevant genes when they have been identified, as well as for the associations between the SNPs and the presence of the disease. If granted, such patents would give control over the use of the DNA sequences for more complex and arguably more important uses, such as identifying biochemical pathways in disease and drug targets within those pathways.

- 5.7 The example of BRCA1, and the fact that many more diagnostic tests for both diseases associated with a single gene and, possibly, more genetically complex diseases are likely to be developed, raise questions about patenting DNA sequences in this area of activity. In this section therefore, we examine whether, in the first place, patents for diagnostic tests that assert rights over DNA sequences do indeed meet the legal criteria for patenting, as has so far been thought by patent offices. We then examine whether the overall effect of allowing such patents will be beneficial to society, and ask what are the arguments in favour of continuing to grant patents in the field of diagnostic tests based on DNA sequences.

Do diagnostic tests based on DNA sequences meet the legal criteria for patenting?

- 5.8 We suggested in Chapter 3 that the fact that genes are essentially a form of information makes the issue of their eligibility for patenting very different from that involved in the isolation of other chemical compounds. In the case of diagnostic tests, this issue is particularly pertinent, since it can be argued that what is claimed as an invention is the fact that an association exists between a gene variant and a disease. The knowledge about the DNA sequence of the gene and the disease-associated mutations is applied by using it as a basis for detecting and characterising the gene in the patient.³ As knowledge of the biological function of the gene is not necessary for its diagnostic application, the owner of the patent does not need to take account of this. Thus, the description of an association between a gene and a disease amounts to little more than a discovery.
- 5.9 However, as we have noted, (paragraph 3.10) in general, the law in most countries has been generous in effectively allowing the applications of discoveries to be regarded as inventions provided that they are useful. It could be argued that this lack of a clear distinction between a discovery and an invention is in the public interest, because incentives are required to encourage the development of discoveries that are useful into products. This may indeed sometimes be the case. However, where the discovery is routine and the prospective use speculative, the owner of the patent stands to gain a reward which may not be commensurate with his contribution.
- 5.10 We accept that at the time that genes such as BRCA1 were patented, their identification required greater ingenuity, effort and resourcefulness than is required to isolate a gene today. Despite the effort involved, we consider that the isolation of BRCA1 was essentially a discovery, the application of which was useful. For the majority of patent offices, this criterion is, in practice, the overriding determinant of whether an invention is patentable. Indeed the non-inventive isolation of a chemical compound is not regarded in patent law as a critical factor for patenting provided that useful properties are identified.
- 5.11 We note however, that now that the human genome has been sequenced, the isolation of a DNA sequence and the identification of its association with a disease are significantly more straightforward. Furthermore, inferring a possible function for a DNA sequence, by

³ This process is achieved by designing short pieces of DNA called primers which are based on the ends of the DNA sequences. The patient's DNA sequence is then amplified using these primers and the PCR process. The copies of the patient's DNA sequence are then characterised by a DNA sequencing machine.

analogy with another sequence for which some information about its function is known, is relatively routine. In such cases, the EPO has indicated that *in silico* identification of genes would not be regarded as inventive, as this activity would be one that was an obvious step for others to take (paragraph 3.32). **We agree that rights asserted over DNA sequences that have been identified and characterised only by *in silico* analysis of the DNA sequence and comparisons with other identified sequences should not be allowed, on the grounds of lack of inventiveness.** This applies to DNA sequences not only as they are used in diagnosis, but also as research tools and for use in gene therapy.

Does the granting of patents on diagnostic tests based on DNA sequences cause adverse effects?

- 5.12 We have already noted that one of the benefits of the patent system is that scientific knowledge about new inventions is put into the public domain, enabling others to develop further inventions and improvements. For most inventions, it will be possible to invent another product that has a similar function, but which is put together in a different way from the existing inventions, such that it does not infringe the patent. This is known as 'inventing around'. Examples of this include electrical appliances such as vacuum cleaners, where numerous different styles and models have been developed, which all perform essentially the same function, but with varying advantages and disadvantages.
- 5.13 When developing products based on genetic material, however, this concept of 'inventing around' is harder to apply because there may be no alternatives to the naturally-occurring DNA sequences. In the case of diagnostic tests, any test for a gene associated with a disease will need to identify whether one of the many mutations in the relevant sequence is present in the individual being tested and will, therefore, have to involve comparison with the DNA sequence of the normal gene. Moreover, if a patent also claims the products expressed by the gene in question, which would include the proteins which the gene encodes, any alternative tests developed by others based on identifying the presence of such proteins in an individual would require a licence from the holder of the patent.
- 5.14 A second problem as regards some patents on diagnostic tests based on DNA sequences is that an excessively broad patent that contains claims to *all* conceivable diagnostic tests creates a monopoly, such that there is little incentive to develop improved tests. (We use the term improved in the sense that improved tests may be either more comprehensive in the number of mutations they can identify, or less comprehensive but more cost-effective). We consider that the argument based on cost-effectiveness is particularly important in tests designed to screen the population, when there is often a need for compromise between the possibility of missing a proportion of abnormalities and the overall cost. A comprehensive test for all mutations might be appropriate in some situations and not in others. We consider that this is a judgement that should be made on grounds of public health.
- 5.15 The difficulty in developing improved alternatives to diagnostic tests based on DNA sequences that do not infringe the original patents, which may assert broad rights over the DNA sequence or its use in all areas in which it can be used in diagnosis, is potentially serious. Indeed, one study in the US indicates that research on genetic testing has been inhibited by patents on DNA sequences: almost half of the research laboratories which were surveyed have ceased to pursue such research because of existing patents.⁴ Another US study found that as many as 30% of laboratories have discontinued or not developed genetic

⁴ Cho MK. Ethical and legal issues in the 21st century. In: Preparing for the millennium: laboratory medicine in the 21st century, December 4-5, 1998. 2nd ed. Washington, DC: AACC Press; 1998. p. 47-53.

testing for haemochromatosis because of exclusive licensing of patents that assert rights over the most common mutations in the gene involved.⁵ This state of affairs may create too great a monopoly, inhibiting innovation rather than stimulating it. In the US, draft legislation has recently been introduced which would provide an exception for the infringement of patented genes. The Bill would amend patent law so that it would not be an act of infringement to use knowledge about a DNA sequence that had been patented for the purposes of diagnostic testing or research. This exemption would not apply, however, to any individual who was directly engaged in the commercial application of the patented gene. It seems unlikely however, that the Bill will become law.⁶

- 5.16 As well as potentially restricting the development of improved diagnostic tests, broad patents in this area could also restrict other forms of research. That genes are involved in common diseases is beyond doubt but there is disagreement as to how useful such genes could be in diagnosis (see paragraphs 5.5 – 5.6). It is widely acknowledged, however, that understanding the role of a large number of genes in a wide range of common diseases and biological pathways will be of crucial importance for research into new medicines. The possibility that many of these genes, or the SNPs associated with them, will be patented at an early stage of research is likely to limit significantly the freedom of other researchers, particularly those in the pharmaceutical industry. They may be prevented from developing and applying what is essentially scientific knowledge for the purpose of creating new medicines and other products relating to healthcare. The considerations above lead us to ask two further questions: are patents on diagnostic tests based on DNA sequences needed? And, is remedial action required in relation to those patents that have already been granted?

Are patents on diagnostic tests based on DNA sequences needed?

- 5.17 We have seen that under the current patent system in the US, Europe and several other countries, DNA sequences for the purpose of clinical diagnosis have been found both to be eligible for patenting and to meet the relevant legal criteria. We now consider whether this is in the public interest. A central point is whether the enjoyment of a monopoly in relation to a test for a particular gene associated with a disease by one company or other organisation serves the interests of society better than does a competitive market in which there are a number of tests for the same genetic disorder.
- 5.18 One argument in favour of the proposition that patents are needed in this area is that without the protection of the patent system, the invention and development of new diagnostic tests would be seriously hampered. Although the human genome has been sequenced, locating a particular gene does not itself lead directly to a test being available. Developing a genetic test, once the gene associated with an inherited disease has been identified, is sometimes a routine and relatively straightforward task. This may not be the case, however, when the testing of very large genes, multiple mutations, or multiple genes or fragments of genes is required. It may require significant effort to convert the basic knowledge of genetic structure into a clinically applicable, reliable, diagnostic test, although the investment required is unlikely to approach that needed for bringing a medicine through the regulatory process to market. In such cases, some kind of incentive for the development of these diagnostic tests, in the form of protection through the patent system, will be required.

⁵ Merz JF, Kriss AG, Leonard DGB, Cho MK. Diagnostic testing fails the test. *Nature* 2002;415:577-579.

⁶ H.R. 3967; "Genomic Research and Diagnostic Accessibility Act of 2002" (current information about this Bill is available from Thomas: legislative information on the internet. <http://thomas.loc.gov/> (24 Jun 2002)).

- 5.19 In discussions concerning the question of whether DNA sequences meet the legal criteria for patenting, most consideration has been devoted to the use of DNA sequences as the basis for diagnostic tests for predisposition to inherited disease. However, diagnostic tests based on DNA sequences are increasingly being used in diseases which are acquired, rather than inherited, for example in determining the genetic changes underlying particular cancers, or in examining the patterns of gene expression in various diseased tissues. Some way of encouraging the development of such complex diagnostic tests, both for inherited and acquired diseases, is in the general interest of society.
- 5.20 In other areas of diagnostic testing, broad protection by patents has not been shown to be vital. Many conventional diagnostic tests for a wide range of diseases and disorders have used the presence or absence of other molecules such as proteins as a means of detection. By comparison with medicines, the costs of research and development in the case of diagnostic tests have been relatively low, the time for development relatively short, and the impact of regulation much reduced. Consequently, there has been less need for the economic incentives afforded by patent protection. In addition, some diagnostic tests have not been patented because they involve chemical compounds that are already known, such as cholesterol. Others have been protected by use patents (see Box 3.1), which confer protection on the method used, but not on the compound on which the test is based. That said, there are, however, some tests that have been granted relatively strong patent protection, including claims to the compound that is detected, as, for example, in the case of the prostate specific antigen (PSA) test for prostate cancer.⁷ But, as we argued earlier in the case of diagnostic tests based on DNA sequences, it can be suggested that what has been discovered here is not a product, but the fact of an association between a protein and a disease. We consider that the knowledge of its association with prostate cancer is in essence a discovery and that the application of that knowledge in the form of a diagnostic test, although useful, may be viewed as obvious. However, as the discovery of associations between proteins and diseases is much less straightforward than between DNA and diseases, and the techniques less generic, the argument that the associations are obvious is not clear cut.
- 5.21 A further argument in favour of protection through the patent system that has been suggested to us concerns research and development in the relatively new area of identifying genes which may be used to diagnose, or predict the occurrence of, common diseases. Many genes that each exert a small effect are likely to be involved in such diseases. Research into the genetic basis of such diseases is much more expensive than research and development for diseases associated with a single gene, as the method used is time-consuming and characterised by a high degree of uncertainty.⁸ Without the promise of strong protection through the patent system, it is argued that investment in this particular area by privately-funded organisations could be expected to decline and that patients, as a consequence, may be denied potentially valuable diagnostic tests. We are not persuaded by this argument. We note that there are other approaches which could, in the future, offer inexpensive, rapid predictive knowledge relating simultaneously to more than one disorder, based on the straightforward and valid use of patented *technologies*, rather than what is essentially patented *information*. For example, the development and application of patented technologies such as DNA microarrays have considerable potential for the precise diagnostic classification of cancer. These devices contain

⁷ The PSA test is a blood test that measures the level of prostate specific antigen, a protein produced by the prostate gland. A high level of PSA usually indicates a prostate problem, though not necessarily cancer.

⁸ For a discussion of the problems and criteria concerning the verification of a verified SNP-disease association see Freely associating [editorial]. *Nat Genet* 1999;22(1):1-2.

thousands of DNA sequences in an ordered array, which allows simultaneous analysis of a similar number of genes⁹ or marker regions of DNA that are closely associated with genes. As things stand, the application of these technologies could be obstructed by the grant of many patents claiming human DNA sequences, many of which will overlap, or relate to different mutations of the same genes.¹⁰ With the grant of such patents, the negotiation of licensing to allow simultaneous testing for more than one disorder is likely to be complex, uncertain and expensive. Here too, the award of broad patents that assert rights over DNA sequences may inhibit rather than facilitate the development of diagnostic tests based on DNA sequences.

How should the system be amended for the future?

5.22 We have argued above that allowing property rights to be asserted over all uses, or even all diagnostic uses, of DNA sequences for diagnostic tests based on DNA sequences gives inventors too great a monopoly in the light of the contribution and inventiveness of their product, may hamper innovation and may not, in fact, satisfy the legal criteria for patenting. We think it likely that, if left unchanged, the patent system as it is currently applied to DNA sequences in the case of diagnostic tests will have a deleterious effect on the development and use of such tests. In view of this conclusion, we consider that the criteria for patenting DNA sequences as they apply to diagnostic tests based on DNA sequences should be applied more stringently or amended. Patent offices should critically assess whether the isolation of DNA sequences, in particular human DNA sequences, can any longer be viewed as inventive (see paragraphs 3.29 – 3.34). We take the view that in the majority of cases, this criterion will not be met. We recognise, however, as observed above (paragraph 5.18), that there will be circumstances in which significant effort will be needed to develop a diagnostic test and protection through the patent system will be required. **We recommend that the criteria already in place within existing patent systems for the granting of patents, particularly the criterion of inventiveness, be stringently applied to applications for product patents which assert, inter alia, rights over DNA sequences for use in diagnosis. We recommend that the European Patent Office (EPO), the United States Patent and Trademark Office (USPTO) and the Japan Patent Office (JPO) together examine ways in which this may be achieved.** If this recommendation were to be implemented, we expect that the granting of product patents which assert rights over DNA sequences for use in diagnosis would become the rare exception, rather than the norm. Where the application of the criterion of inventiveness is not particularly stringent, as for example in the US, additional mechanisms may be needed. **We recommend, accordingly, that the USPTO and US lawmakers give consideration to whether patent laws need to be amended for this purpose.**

5.23 One of the main concerns about asserting rights over a DNA sequence in a product patent is that the patent owner has exclusive rights to all subsequent uses of that sequence. One option that is often suggested as a way to avoid the deleterious effects of this, is to limit patents on diagnostic tests based on DNA sequences to use patents, that is, patents which do not assert rights over the DNA sequence itself. It has been argued that the DNA sequence would be freely available for other researchers to develop new products, without having to negotiate a licence. In contrast, a product patent on a diagnostic test for a gene would allow the patent owner a monopoly on all uses of that sequence for any sort of test or other application. For example, if BRCA1 were found to be linked to heart disease, or cancer of

⁹ Occurring in the form of cDNA sequences.

¹⁰ See testimony of Caulfield, B to the US Federal Trade Commission and Department of Justice. <http://www.ftc.gov/opp/intellect/020319barbarcaulfield.pdf>. (24 June 2002)

the bladder, the rights of the owner of the product patent would extend to these new diagnostic tests or other applications.

- 5.24 A broad use patent for a diagnostic test for BRCA1 that referred specifically to breast cancer, would give the owner rights over all testing for that genetic susceptibility to breast cancer, but not for other diseases. However, the effect of the patent owner having broad property rights over the diagnostic use of the gene for just one disease, would be that the patent owner has a monopoly over all ways of testing for that disease. This is because, even though the use patent does not include the sequence itself in the patent claims, in practice, any other diagnostic test for the disease specified in a use patent would infringe that patent.¹¹ The fact that one of Myriad Genetics' patents relating to the BRCA1 gene which has been opposed at the EPO is a use patent, serves to illustrate this important point.¹² However, if a use patent could be defined, so that the owner of the patent is entitled to rights only to the use of the DNA sequence for his specific diagnostic test for the disease in question, and not *all* diagnostic tests for the disease involving the use of the sequence, this could, on the one hand, provide sufficient incentive for the company to develop the test, and on the other, result in the development and marketing of a number of different tests for the same gene. **We conclude that the protection by use patents of specific diagnostic tests which are based on DNA sequences could provide an effective means of rewarding the inventor while providing an incentive for others to develop alternative tests.**

Should compulsory licensing be required in relation to patents that have already been granted?

- 5.25 What if patents have already been granted? The traditional response is for others to purchase a licence to use that which is patented. But what if the owner of a patent is unwilling to offer a licence at a cost which is reasonable to the providers of healthcare or other prospective licencees?
- 5.26 One possible way of ameliorating this state of affairs is through the introduction of compulsory licensing. Because genetic information cannot easily be 'invented around', we consider that the exclusive rights of exploitation that are created by the patent system differ, at least in degree, from the exclusive rights that other patents create. Thus, when a patent is granted, should there be any kind of duty to license it to those who request it? The law imposes no duties on the owner of a patent. What the law does, in some circumstances, is to impose sanctions on owners of patents who do not exploit their invention, or otherwise abuse their monopoly. Such sanctions are in part imposed by specific provisions of patent law, for instance the conferring of a right to a compulsory licence at a reasonable cost when there is no exploitation by the owner of the patent, or when the owner is unwilling to license. Other sanctions result from the general law of competition. In practice, however, compulsory licensing is rarely imposed.
- 5.27 We consider that the more important issue for public policy here is not whether the invention meets the criteria for eligibility and the legal criteria for patenting, but the *effect* of the virtual exclusive rights. If the monopoly enjoyed is such that an important diagnostic tool is only available from the inventor at what is judged to be a high cost, who is unwilling to license others who could provide a cheaper alternative, an appropriate remedy may be

¹¹ It may be argued that alternative diagnostic tests could be developed which test the protein produced by the gene, rather than the gene itself. However, if use patents claiming the use of a gene also include claims to the use of the expression products of the gene, as they often do, such a test would still infringe the patent.

¹² European patent EP0699754.

the compulsory licensing of the patent involving the DNA sequence at a reasonable cost. The right of governments to impose compulsory licensing on medical inventions to protect public health has recently been affirmed by the WTO in the Doha Declaration.¹³ **However we note that the circumstances under which compulsory licensing may be considered have narrowed under the TRIPS agreement. Thus, the statutory framework in some member countries, including the UK, may need adjustment to allow the consideration of compulsory licensing to deal with cases such as those in which exclusive rights to the diagnostic use of a DNA sequence may not be in the public interest.**

- 5.28 The arguments against compulsory licensing are that it will decrease the incentive to develop new inventions, and encourage secrecy among inventors: in other words, the beneficial effects of the patent system will be lost.¹⁴ However, we consider this a weak argument. If the monopoly inherent in the patent system as it relates to diagnostic tests based on DNA sequences is having a deleterious effect on society overall, then any remedy, to be effective, must necessarily involve a weakening of the monopoly awarded in this area. The question of policy, therefore, is: will the deleterious effects of making some inroad into the protection provided by the patent system outweigh the beneficial effects?
- 5.29 Opposition to compulsory licensing is particularly strong in the pharmaceutical industry at a time when the costs of research and development are rising and the rate of production of new medicines is falling. Moreover, there is a view more generally that once compulsory licensing is deployed in one sector, the principle will be more readily applied elsewhere. We recognise the dilemma: in the case of medicines generally, there are those that are too expensive to be made available for all of the patients who need them; but the widespread imposition of compulsory licensing could seriously erode the capacity for research and development of the pharmaceutical industry. A careful balance would, therefore, need to be struck so that compulsory licensing is only invoked in those cases in which the existence of a monopoly is creating an unacceptable and unfair situation. The guiding principle here would be that the protection which was granted by the patent system should be commensurate with the contribution made by the inventor. In fact, extensive application of compulsory licensing in relation to diagnostic tests may not be required, as experience has shown that the mere threat of compulsory licensing has been sufficient to encourage industry to devise other solutions.¹⁵ We do not, therefore, support a wholesale and

¹³ The TRIPS Agreement contains clauses which allow for parallel imports and compulsory licences. Article 31 deals with provisions for the use of patents where authorisation has not been obtained from the owner of the patent. Of these provisions, the criterion of individual merit and the condition that attempts have been made to reach reasonable commercial terms with the patent owner within a reasonable period of time are most relevant. The Article further provides that this latter condition may be waived in the case of a national emergency, other circumstances of extreme urgency, or for public non-commercial use of an invention. On 14 November 2001, the Declaration on the TRIPS Agreement and Public Health was adopted at the fourth WTO Ministerial Conference in Doha, Qatar. Whilst reiterating commitment to the TRIPS Agreement, the Declaration affirmed 'that [this] can and should be interpreted and implemented in a manner supportive of WTO members' right to protect public health...' and reaffirmed 'the right of WTO members to use, to the full, the provisions in the TRIPS Agreement, which provide flexibility for this purpose'. Such 'flexibilities' included members' right to grant, and determine the grounds for granting, compulsory licences, and to define what constitutes a condition of national emergency or other circumstances of extreme urgency. The Declaration also called for the TRIPS Council to address the problems which WTO members, with insufficient or no manufacturing capacities in the pharmaceutical sector, may have in making effective use of compulsory licensing under TRIPS. The Council has been asked to report to the General Council on this point before the end of 2002.

¹⁴ Further arguments offered against compulsory licensing include the possibility that such a system will be too expensive and complex to administer, and that the validity of patents will be challenged less frequently because it will be easier to obtain a licence than to dispute the patent, meaning that invalid patents may never be challenged or revoked.

¹⁵ For example in the recent cases of differential pricing of anti-retroviral medicines for the treatment of HIV/AIDS in several developing countries.

indiscriminate use of compulsory licensing. **Rather, in those specific cases in which the enjoyment of exclusive rights to the diagnostic use of a DNA sequence is not in the public interest, we recommend that those seeking to use the diagnostic tool or develop an alternative should seek a compulsory licence from the relevant authorities if they are refused a licence from the owner of those rights on reasonable terms, and we encourage the authorities to grant such a licence.** We also note the suggestion made by the Organisation for Economic Co-operation and Development (OECD) of a 'clearing house' to ease the obtaining of licences for 'genetic inventions' by commercial laboratories.¹⁶ We suggest that this concept, which might reduce transaction costs, should be explored further.

2. Research tools

Background

5.30 Over the past few years, there has been a marked increase in the number of patents that assert rights over DNA sequences that fall into the category of research tools.¹⁷ We describe these sequences as research tools because they are of use in research, but generally have no immediate therapeutic or diagnostic value. In other words, what is being patented is a research tool, to be used principally as a means of developing a commercial product, such as a medicine or vaccine, rather than constituting a product in itself. Such DNA sequences may consist of entire genes, parts of genes or just a few base pairs. Very often, the function of the encoded product of the gene may not have been fully elucidated. Some of these sequences may have the potential to yield commercial products in the future when their function is better understood. One of the most important applications of this kind of genetic information, however, is to identify potential targets for the purpose of designing new medicines. In this section we first consider the kinds of DNA sequences which fall into the category of research tools and how they are being identified, patented and used. We then consider whether patents in relation to this category of DNA sequences are legally justified, and finally if they are necessary to promote the public interest.

The kind of DNA sequence

5.31 Any DNA sequence which has a use in research can be classed as a research tool. As we have said, these sequences will generally not have any immediate diagnostic or therapeutic use. Two particular types of research tool are ESTs and SNPs. The development of the EST approach, whereby the coding parts of genes could be rapidly sequenced, led to the extensive application of this method as a means of locating entire genes. Now that the sequencing of the human genome has been completed, many genes of unknown function are available for study. Access to these data is accelerating our understanding of disease. SNPs are also important research tools which are used in research to help locate genes associated with disease or identify genetic variation which may predispose to disease. The pharmaceutical industry has a major interest in applying this knowledge to the process of discovering and developing medicines. By understanding the role of the products of particular genes and their mutations in cellular pathways, ways of modifying their effects can be sought through the action of medicines. (See paragraphs 3.40 – 3.43 for further details regarding ESTs and SNPs.)

¹⁶ Organisation for Economic Co-operation and Development. Short summary report of the workshop on Genetic inventions, Intellectual property rights and licensing practices, Berlin, Germany, 24-25 January 2002. Available at <http://www.oecd.org/pdf/M00031000/M00031448.pdf>

¹⁷ See Footnote 1 for the definition of research tools which we use.

Patenting DNA sequences as research tools

- 5.32 Although we are not aware of any systematic analysis of the ownership of patents which assert rights over DNA sequences which essentially are claimed as research tools, biotechnology companies which specialise in genomics appear to have been the most active in filing patent applications, and many of these have been granted. In addition, some pharmaceutical companies such as SmithKline Beecham, now GlaxoSmithKline, which invested in genomics at a relatively early stage of the development of the field, are believed to have secured a relatively strong position in this area as regards rights to intellectual property. As we have noted (paragraph 1.6), publicly-funded bodies have come under increasing pressure to put findings from research to commercial use, both in the US and, more recently, in Europe. In universities, the acquisition of patents is now recognised as a proper indicator of academic performance and, in response, many researchers in the life sciences have been granted patents in relation to a wide range of DNA sequences. Indeed, as we have noted, it is now the case that in the US, more patents on DNA sequences have been granted to those carrying out research in universities than by industry.
- 5.33 In general, owners of patents on research tools may realise commercial value from their patents either by licensing patents for particular sequences, as in the case of CCR5 (Chapter 4, case study 2), or by applying the knowledge within the institution to programmes aimed at discovering new drugs, or other research. Some companies have been very active in filing patent applications for large numbers of sequences, many of which probably fall into the category of research tools. For example, in 2000, the US company Incyte Pharmaceuticals, had made claims in relation to over 4,500 human DNA sequences in more than 570 patent applications, whilst the US company Human Genome Sciences (HGS) had filed 450 patent applications with claims to more than 34,000 sequences.¹⁸

Do research tools meet the criterion of utility?

- 5.34 We concluded in paragraph 5.11 that rights asserted over DNA sequences that have been identified and characterised only by *in silico* analysis of the DNA sequence and comparisons with other identified sequences should not be allowed on the grounds of lack of inventiveness. If a DNA sequence for use in research does meet the criterion of inventiveness, is it also likely to meet the criterion of utility? A major concern arising from the granting of patents relating to DNA sequences for use in research is that they give a level of protection which, in our view, is not reflected in the extent of the contribution made by the applicant. Such an outcome is clearly illustrated by the case of the CCR5 receptor (Chapter 4, case study 2) whereby a broad US patent was granted to the company HGS, even though it was unaware of the actual role of the receptor in HIV/AIDS. It could be argued that patent protection for research tools such as the CCR5 receptor is justified because the owner of the patent has contributed more than mere knowledge of the DNA sequence and speculations about its associations. The owner has, in fact, described the protein that the DNA sequence encodes, suggested a possible function for that protein and indicated how it might be used. That said, there is no doubt that low thresholds for utility and inventiveness have been applied in many hundreds if not thousands of patents that assert rights over DNA sequences. **We consider that such claims, which amount to routine discoveries with weakly demonstrated or speculative uses, will seldom deserve the status of patentable inventions.**

¹⁸ Stokes G. Lies, damned lies, and statistics. Patent applications on genetic sequences – on the up and up. IP Matters [online forum]. Apr 2000. Available from: <http://www.derwent.com/ipmatters/statistics/genetics.html> (24 June 2002)

Using research tools that have been patented

- 5.35 The pharmaceutical industry and biotechnology companies which carry out research into the development of new medicines are likely to be the main users of DNA sequences as research tools. The process of discovering new medicines can involve testing libraries of potential medicines against biochemical sites or targets to see if there is any interaction. This early-stage screening process can involve a broad range of genes and their expression products, particularly those that code for receptors.¹⁹ As the research progresses, the range of genes which show activity of potential interest will narrow to a relatively small number.
- 5.36 An organisation which is using a DNA sequence over which rights are asserted in a patent for commercial research and development must seek a licence before doing so. Opinion differs within the pharmaceutical industry as to the effect of this on the discovery of new medicines. Some companies take the view that the additional costs incurred through the need to take out large numbers of licences on DNA sequences for use in research are not significant. Others consider that the costs incurred are already having a significant impact on profit margins. These differences of view most likely reflect the extent to which individual companies own patents that assert rights over DNA sequences. Access to research tools based on DNA sequences may indeed prove to be difficult and expensive unless the patents that protect them are licensed easily and widely.
- 5.37 However, from a legal perspective, it is currently an open question as to whether the use of a patented DNA sequence by another party for the purposes of drug screening would actually amount to infringement and whether damages should be levied. One view is that the use of research tools in this way falls under the research exemption (paragraphs 5.43 – 5.45) and that there would therefore be no infringement. Another view is that there would be infringement but that damages should only be set at the level of the cost of a research licence. A further view is that the infringement should result in damages which are reflected in the value of the product. It is an accepted principle of the patent system that the monopoly awarded to an inventor should reflect the contribution that he has made. In this situation, we consider the claims in a patent that asserts rights over DNA sequence which has a use in drug screening should not ‘reach through’ to the product. By ‘reach through’, we mean the capacity the owner of a patent has to claim rights over further unrelated uses identified by researchers at a later stage.
- 5.38 If rights in relation to a partial DNA sequence or EST are asserted in a patent, it is possible that the patent will also extend to the full DNA sequence, even though the full sequence may be isolated by someone else without using the EST in question. This possibility of ‘reach through’ by ESTs to whole genes has been one of the principle concerns of those who have objected to the idea that ESTs may be patentable (paragraph 3.42). There is wide agreement that patent protection of partial DNA sequences such as ESTs should not be granted in broad terms. **We recommend that when rights are asserted in terms intended to cover all sequences that contain the EST that is the subject of the original patent, no patent should be granted.**²⁰ We endorse the serious concerns expressed by the Human Genome Organisation (HUGO) about the deleterious effect on further progress of genetic research and the successful exploitation of its results, should broad claims within patents of the so-

¹⁹ Receptors are molecular structures located within cells or on the cell surface which serve as sites for specific molecules to bind to. They are often effective drug targets and companies will screen libraries of potential medicines against them.

²⁰ For example, a patent claim to ‘An isolated DNA sequence comprising [or including or having] the sequence of SEQ ID NO:1’ is much broader than a claim to ‘An isolated DNA sequence consisting of the sequence of SEQ ID NO:1’, as by long established practice the former wording permits additional sequences to be present whereas the latter wording does not.

called 'having' and 'comprising' type be issued for ESTs. We endorse the call of HUGO to patent offices not to issue patents on ESTs without having found balanced solutions for the problem of dependent patents.²¹ (A dependent patent is one whose exploitation would encroach upon the exploitation of an earlier patent.)

5.39 There are various ways in which patents on DNA sequences which have a primary use as research tools may inhibit innovation and development:

- the cost of research may increase, as the grant of increasing numbers of patents will mean that ever more licences are required before research can be conducted;²²
- research may, as a matter of practice, be made more difficult if researchers are required first to negotiate the use of patented genes and sequences;
- a patent owner may withhold a licence to gain maximum financial benefits, or licence it exclusively to one or a limited number of licencees;
- companies that wish to acquire the rights to several DNA sequences may decide not to develop a therapeutic protein or diagnostic test because of the number of royalty payments that would be required (this is sometimes referred to as royalty-stacking);²³

5.40 There is insufficient evidence to judge the extent to which the granting of patents that assert rights over DNA sequences based on a primary use as research tools is producing the potentially deleterious effects set out above. However, we take the view that the exercise of a monopoly over what are now essentially discoveries of genetic information accessible by routine methods is, in principle, highly undesirable. We consider that the development of a culture among those who carry out scientific research, whereby claims are made to naturally-occurring material which can be isolated by routine procedures and to which a weakly demonstrated or hypothetical utility may be ascribed to secure some possible future value, if endorsed by the patent offices, amounts to a misapplication of the patent system.

5.41 **We consider, therefore, that in general, the granting of patents which assert rights over DNA sequences as research tools should be discouraged.** In this way, the state of affairs which arose in the case of CCR5 (Chapter 4, case study 2) is avoided, whereby a substantial reward is given to the applicant in the form of exclusive rights to *all* uses of a DNA sequence in return for a relatively minor scientific effort. We consider that the best way to discourage the award of such patents is by a stringent application of the criteria for patenting, particularly that of utility. **We therefore welcome the recent Utility Guidelines for DNA sequences introduced by the United States Patent and Trademark Office (USPTO), which have, in effect, been endorsed by the European Patent Office (EPO).**²⁴ We have noted that these Guidelines require when rights are asserted over DNA sequences in patent applications, a substantial, credible and specific use must be demonstrated (see paragraph 3.36). We have also suggested that such uses must be more than theoretically possible. In other words, there must be some evidence for the specific and

²¹ HUGO. HUGO Statement on patenting of DNA sequences - In particular response to the European Biotechnology Directive. London: HUGO; 2000.

²² This creates a particular problem for the pharmaceutical industry, which is likely to be most dependent on the use of patented research tools in the form of DNA sequences and genes.

²³ There is also the potential for a patent owner to restrict the licensee's exploitation of an

²⁴ USPTO Utility Examination Guidelines Fed. Reg. 66: 1093. 5 Jan 2001. <http://www.uspto.gov/web/offices/com/sol/notices/utilexmguide.pdf> (20 May 2002).

substantial utility claimed in order for it to be credible. We consider that the introduction of the Guidelines should go some way to mitigate the tendency of some patent offices to allow rights in relation to DNA sequences to be asserted when any demonstration of utility is, at best, weak. However, it is not yet certain whether the Guidelines will prove to be sufficient: they have only been in operation for 18 months. **We recommend, therefore, that the United States Patent and Trademark Office (USPTO), the European Patent Office (EPO) and the Japan Patent Office (JPO) should monitor the impact of the Guidelines on the examination of patents to ensure that the criterion for utility is rigorously applied so that the grant of a patent more properly reflects the inventor's contribution. If this proves not to be the case, the Guidelines should be reviewed and strengthened to achieve this purpose.** Taking further corrective action (if it is needed) cannot be allowed to wait unduly long. As we observed in the case of DNA sequences as they are used in diagnosis (paragraph 5.42), we expect that if this recommendation were to be implemented, the result will be that patents which assert rights over DNA sequences for use in research will become the rare exception rather than the norm.

Licensing DNA sequences for research

- 5.42 We have noted that many organisations, particularly universities and biotechnology companies, have already been granted patents in relation to DNA sequences which have a primary use as research tools. Such organisations are often not well placed to undertake extensive product development and distribution and will often seek to realise the value of their patents through licensing. Under these and other circumstances, the risk arises that an important patent may be licensed exclusively. The resulting exclusivity may not be in the public interest: it may discourage others from working in an area which would profit from a variety of approaches or solutions. **We recommend that those public institutions which already have been awarded patents that assert rights over DNA sequences as research tools be strongly encouraged not to licence them exclusively to one or a limited number of licencees, even when, by not doing so, they may suffer some loss of revenue in the short term. We also recommend that, wherever possible, the private sector should consider non-exclusive licensing for those DNA sequences which are used in research.**

The research exemption

- 5.43 Many researchers want to make use of patented DNA sequences in research when there is no obvious prospect of commercial development arising from that use. This situation will arise in the context of most academic research, as well as some research in industry. Research may be undertaken on inventions which have been patented, including DNA sequences. This is generally referred to as the 'research exemption'. Most patent systems have some form of exemption to enable research to be carried out on a patented invention provided it is not intended to produce commercial benefit, so as to ensure that innovative research is not stifled.
- 5.44 The precise scope of the exemption varies between countries. In Europe, the legislation in most countries has some form of research exemption, exempting from infringement research that is conducted on a patented invention (as opposed to the use of a patented invention in the course of research, which is not exempted). The Community Patent Convention (CPC) states in Article 27(b) that the rights conferred by a patent 'shall not extend to acts done for experimental purposes relating to the subject-matter of the patented invention'. The CPC has not been implemented but the national patent laws of many European countries have similar wording. Japanese patent law states that 'the effects of the patent right shall not extend to the working of the patent right for the purposes of

experiment or research'.²⁵ However, in the US, there is no such statutory research exemption. US common law recognises a limited exemption for scientific experiments, but the application of the exemption varies, and, that being the case, requires clarification. Even in Europe, where there is a statutory basis for the research exemption, the scope of the exemption is not clear.²⁶

- 5.45 We consider that the concept of the research exemption is very important, particularly in the area of research involving the use of genetic information. The knowledge embodied in patents claiming DNA sequences should, in our view, be freely available for all scientists to apply in the pursuit of non-commercial research. **We recommend that the 'research exemption' is given a statutory basis in the US and clarified in Europe by policy-makers as a matter of urgency.** We recognise that when such knowledge from an existing patent is used for commercial purposes, the researcher is obliged to acquire a licence from the patent owner. However, as we have seen, several thousand patents which assert rights over DNA sequences have already been filed and may yet be granted (paragraph 5.33). The need to seek multiple licences for many such sequences may hinder research and development. **We further recommend that companies work together to extend the concept of the 'research exemption' throughout industry for DNA sequences which appear in patents and which have a use in research.**

3. Gene therapy

Background

- 5.46 Some diseases are caused by mutations, or mistakes, in the human genome. A particular disease can be caused by a number of different mutations in the same gene. For example, there are as many as 1000 known mutations in the gene responsible for cystic fibrosis. The idea of correcting a faulty gene by replacing it with a normal version of the gene has been the focus of several research programmes in gene therapy over the last 15 years. There are serious technical difficulties in trying to introduce normal genes into the human body, which will then function sufficiently well to reverse the symptoms of a disease. Progress in research has been slow and success very limited, although there has been recent progress in treating severe combined immunodeficiency (SCID) and haemophilia B.²⁷ Despite these difficulties, a wide range of patents have been granted to protect both the methods and materials associated with gene therapy.
- 5.47 Any treatment based on gene therapy will require the use of a DNA sequence. If the gene is patented, treatment for gene therapy will depend, at least in part, on the availability of a licence from the owner of the patent. For example, a genetic therapy for cystic fibrosis would depend on whether a licence could be obtained from the principal owner of the patent that relates to the gene responsible for cystic fibrosis.²⁸ Many patents which assert rights over human DNA sequences include claims to the use of the sequence for gene therapy, even though such applications have almost never been demonstrated. This is because patent applicants have been allowed to assert rights over uses which are judged to be theoretically credible without having evidence from research to show that they have made experimental progress towards realising this theoretically obvious possibility.

²⁵ Patent Law no. 121 of April 13, 1959, as amended by Law no. 220 of December 22, 1999.

²⁶ For example it is not clear whether the research exemption extends to clinical trials. Case law in some countries suggests that it does. In other countries, the contrary is suggested.

²⁷ See for example Rosen FS. Successful gene therapy for severe combined immunodeficiency. *N Engl J Med* 2002;346(16):1241-3.

²⁸ The principal owner of the patent relating to the cystic fibrosis gene is The Hospital for Sick Children in Toronto.

- 5.48 We have already concluded that the association of a gene with a disease or condition is essentially a discovery of genetic information. In the case of gene therapy, the information entailed in that discovery is applied by using the DNA sequence itself as a medicine. Today, identifying a gene and suggesting that it could be used for the purposes of gene therapy (amongst other uses) would appear to a reasonable person not to meet the legal criterion of inventiveness, and thus, not to warrant the grant of a patent. However, the development of methods to introduce genes into the patient continues to require novel and inventive approaches which in general merit patent protection.
- 5.49 Is the granting of a product patent in relation to the DNA sequence necessary to ensure that the treatment would be developed? We accept that the development of a medicine without patent protection is rarely a practical proposition. In the context of gene therapy, there will be substantial costs associated with the manufacturing of materials for delivering the gene into the patient, and with the safety precautions involved in testing treatments in patients. However, too much protection may have a perverse effect. It may be too expensive to develop some gene therapies where several licences, for both the genes and the technologies, would have to be secured before the therapy could be made available, especially if the demand for the therapy were relatively small. **We consider that once a gene associated with a disease is identified, the use of the relevant DNA sequences in gene replacement therapy, to alleviate the effects of mutations in that gene, is obvious (particularly when such use is claimed on a purely speculative basis). Therefore, we recommend that protection by product patents should seldom be permissible.** We can imagine other forms of gene therapy, where some innovation more complex than simply replacing a damaged gene is involved, which may constitute an inventive step. Certainly, some kind of incentive in the form of patent protection is needed to encourage the development of valid and effective gene therapy. It is a difficult area of technology which requires investment. **We believe that patent protection should be concentrated on developing safe and effective methods of appropriate gene delivery.** This is where the real inventiveness and investment will be required, rather than in simply defining the sequence of the genes to be used in treatment.

4. Therapeutic proteins

- 5.50 It is clearly in the public interest to provide the best conditions for innovation as regards the development of new medicines. Patents granted on medicines afford protection in the marketplace and allow the profits generated to be re-invested for the research and development of new medicines. The pharmaceutical industry often cites the very high costs associated with bringing a drug to market through both the processes of discovery and development and the need to meet the various requirements of regulatory agencies as the primary justification for the patent system as regards the industry (paragraph 2.7). We accept that resort to the protection of the patent system in the pharmaceutical sector has been a force for good. Without this protection, enterprises would be unable to provide for the considerable financial risks associated with the discovery and development of new medicines. In this section we examine medicines which are based on naturally occurring DNA sequences which have been approved by licensing authorities. These medicines include Epo, beta interferon and a number of others. Although there are comparatively few of them, some, such as Epo and G-CSF, have been very successful.²⁹

²⁹ For example the US company Amgen Inc. has a G-CSF product, called Neupogen, which had global sales of around US\$1,346.4 million in 2001. Amgen Inc. also has an Epo product, Epogen, which had global sales of just over US\$1,962.9 million in 2001 (Amgen Annual Report 2001).

5.51 It may be argued, in the same way that what is being patented in the case of a diagnostic test based on genetic information is the fact that the gene causes the disease, what is being patented in the case of a therapeutic protein is the fact that the protein causes the disease to be abated. We agree that in both cases, knowledge of the genetic information is a crucial aspect of the product. However, in the case of the protein, the information encoded within the DNA sequence is applied to produce a chemical compound which is produced as a physical substance and administered as a medicine. In the case of the diagnostic test, what is being applied is the knowledge of the association between the DNA sequence and a particular condition.

Are patents that assert rights over DNA sequences needed in the context of therapeutic proteins?

5.52 Patents that assert rights over therapeutic proteins assert rights over the DNA sequence as well as the characterisation of the protein itself. This is because the DNA is crucial to the production of the protein and is regarded as a chemical intermediary in the manufacturing process. Further, in the US, judicial decisions have led to the need to include the DNA sequence in patent claims in relation to a therapeutic protein, so as to show 'possession' of the protein. To secure strong protection for medicines that are therapeutic proteins, it is likely that rights over the DNA sequence must also be asserted.

5.53 Most medicines are based on chemical substances that are not directly derived from DNA sequences. Here, pharmaceutical companies are focused on 'inventing around' the patents of their competitors, conducting research into and marketing medicines that differ sufficiently from the patents protecting medicines that are already on the market. A new medicine must just be different enough from known molecules to be considered novel for the purposes of patent protection, but must also have sufficiently improved properties (or a radically different structure) to satisfy the criterion requiring an inventive step. As a practical matter, it may also have to have similar effects to the medicines already patented so as to be able to compete in the market. This process of 'inventing around' can lead to medicines with significantly improved properties. New medicines that are structurally similar to existing medicines with only minor pharmacological differences are known as 'me-too' medicines.³⁰ 'Me-too' medicines can be developed more cheaply and, once marketed, can produce significant profits for the pharmaceutical company more quickly than developing novel radically new products. However, medicines which are too similar in structure and function to known compounds do not meet the legal criteria for patenting because they lack an inventive step.

5.54 In paragraphs 5.12 – 5.13, we noted in relation to diagnostic tests that it was not possible to 'invent around' a DNA sequence. This is not quite the case with regard to therapeutic proteins. The naturally-occurring DNA sequence can be altered with a view to improving the therapeutic properties of the medicine. For example, an improved tissue plasminogen activator (t-PA) molecule that remains active in the body for a longer period, may well meet the legal criteria for patenting despite the original disclosure of naturally-occurring t-PA in the patent for this therapeutic protein. This might be because it was not clear in the original patent which parts of the molecule could be altered to improve the length of time it remained active. However, if this modified t-PA were marketed, it may still infringe the original patent relating to t-PA because it may literally be within the scope of the claims listed in the patent or be so by virtue of one of the various legal devices which exist to bring

³⁰ There are many examples of 'me-too' medicines: the large number of non-steroidal anti-inflammatory medicines, which includes medicines such as Ibuprofen, is often quoted.

borderline material within the scope of a patent.³¹ In other words, the modified protein (and the modified DNA sequence) may meet the requirements for patenting but the original patent may be sufficiently broad that the modified products fall within it. This means that it is generally difficult to obtain a patent for a modified therapeutic protein when the original naturally-occurring molecule is already claimed in a granted patent.

5.55 Setting aside the legal considerations outlined above (paragraph 5.52), can the assertion of rights over the DNA sequence as well as the therapeutic protein be justified? Are such rights essential? We see no reason why the expressed proteins should not be patented provided that they show novelty, are non-obvious and have utility. The information encoded within the DNA sequence is being applied to define the nature and function of a protein and to develop it into a medicine. We consider that the process of isolating genes that translate directly into tangible products with a specific and readily identifiable use beyond their mere informational content is defensible and analogous to many other examples of patented natural products. We take the view that the benefits to society which arise from the existence of strong incentives, in the form of patents, to produce novel medicines outweigh the possible disadvantages to others of restricting the commercial use of a DNA sequence for the production of a therapeutic protein. Thus, we conclude that patents on therapeutic proteins may assert rights over the relevant DNA sequence.

5.56 We add a caveat. There are many examples of parts of a gene being used, in different permutations and combinations, to produce more than one protein. For example, our immune system works through very large numbers of specific antibodies, based on changed use and arrangement of the genes which code for the antibodies and cell-surface molecules involved. Once a protein has been produced, it will be subjected to various modifications.³² Thus, a diversity of proteins can be produced from a single gene. An excessively broad patent in relation to a DNA sequence which codes for a protein put to some novel therapeutic use could be expected to extend to all proteins coded for by that sequence. **We take the view that while rights asserted over DNA sequences which are used to make new medicines based on therapeutic proteins are generally acceptable, they should be narrowly defined. By this we mean that the rights to the DNA sequence should extend only to the protein described.**

Limiting the scope of patents that assert rights over DNA sequences

5.57 We have considered the justification for granting rights in relation to DNA sequences in four separate categories of use: diagnostic tests, research tools, gene therapy and therapeutic proteins. The recommendations that we have put forward, if they were implemented, would have the effect of substantially reducing the number of product patents that assert rights over DNA sequences. However, there will occasionally be circumstances when product patents may be justified, as in, for example, the case of certain diagnostic tests (paragraph 5.18) and therapeutic proteins (paragraph 5.55). Thus, the problem of the wide scope of such patents remains.

³¹ The extent to which inventions that are similar to ones already patented are covered by a patent is dealt with in law primarily by the wording of the claims contained in the patent. Secondly, many countries have some kind of legal mechanism for determining whether something that is not quite covered by the literal wording of the patent claims should nevertheless be regarded as within the scope of the patent. In the US, the so-called 'doctrine of equivalence' serves this purpose, and in the UK patent claims are interpreted 'purposively' rather than strictly literally without reference to context.

³² In the process of transcription, the genetic code is copied from the DNA to messenger RNA (mRNA). mRNA can then undergo a variety of post-transcriptional modifications that generate different versions of that mRNA, which can in turn yield different proteins. Once the genetic information in the mRNA has been translated to produce these proteins, the proteins can be subjected to a large range of further modifications before they achieve their biologically active forms. These modifications explain, in part, the disparity between the estimated number of genes (30,000-40,000) and the estimated number of proteins (over 300,000) in humans.

- 5.58 We have observed that the law in many countries, including the US and Europe, has tended to be generous in granting patents which assert rights over DNA sequences and, furthermore that the effects of many of these patents are extensive, because inventors who assert such rights obtain protection on all uses of the DNA and, sometimes, also the proteins which the DNA produces. It is a feature of DNA that one gene will often generate more than one product, for example, different proteins. Consequently, finding novel uses for DNA sequences will be a relatively common event. This is not generally the case in other areas of patenting. Thus, a researcher who is granted a product patent in relation to a DNA sequence as a research tool, will also gain the exclusive rights to the use of that sequence in a diagnostic test, as a source of a therapeutic protein, and for gene therapy.
- 5.59 We believe that this state of affairs has encouraged many researchers to apply for patent protection at an earlier stage in the process of discovery than was intended when the patent system was established. Many researchers make patent applications even before the function of the gene has been fully elucidated. The granting of too many broad patents at too early a point in the development of an emerging area of science may restrict others from having access to the genetic information covered by the patents and consequently risks limiting its application. The MSP-1 antigens in Chapter 4, case study 5 are one such example.
- 5.60 The effect of the recommendations which we have made so far in this Paper would be to reduce substantially the number of patents that assert rights over DNA sequences. We consider that if they are granted, there is a strong case to be made for limiting the scope of such patents. If our recommendations are not adopted, then it would be that much more important to develop a mechanism which would limit the scope of product patents. We now put forward a possible approach that would curtail the breadth of some product patents that assert rights over DNA sequences.
- 5.61 The law in the US makes it clear that product patents are not restricted to the particular use which is set out in the claims of the patent, but provide absolute protection for all possible uses. The German Federal Constitutional Court has indicated likewise. These rulings confirm that once an owner of a patent has been granted rights over a DNA sequence, the owner is entitled to exclusive rights to all uses, including uses which have not yet been anticipated or discovered. The rationale for allowing rights to be asserted over all uses of a compound (sometimes called *per se* claims) of any kind, is that the inventor has contributed two things: the compound and the first use for it. While it may be thought that the inventor's contribution does not deserve a monopoly over the compound *per se*, which covers all uses, the law provides for this because the inventor has provided the compound itself for others to work on. In the case of DNA sequences, where the protein produced by the gene is obvious from the sequence, this rationale, of having made a physical compound 'available to others', appears to us to carry little, if any, weight. We take the view that, as a rule, the identification of a DNA sequence as such is generally routine and therefore such extensive rights provide patent owners with rewards that are not justified by the contribution which they have made.
- 5.62 In our view, when patent examiners consider that a patent application that asserts rights over a naturally-occurring DNA sequence meets the criteria for patenting, the applicants could be required in some cases to disclose the specific uses to which they have demonstrated that the sequence can be put. The scope of protection would then be limited to these particular uses. In this way, at the very least, rights over entirely unrelated uses could not be subsequently asserted. The scope of the monopoly awarded would, therefore,

be commensurate with the actual contribution by the inventor. We consider that such a step might avoid the possible deleterious effect of granting product patents, whereby rights to *all* uses of the DNA are acquired, hampering future progress in research on the function of genes.³³ **We recommend, therefore, that the United States Patent and Trademark Office (USPTO), the European Patent Office (EPO), the Japan Patent Office (JPO) and other relevant bodies give consideration to the concept of limiting the scope of product patents that assert rights over naturally-occurring DNA sequences to the uses referred to in the patent claims, where the grounds for inventiveness concern the use of the sequence only, and not the derivation or elucidation of the sequence itself.**

³³ For a more detailed discussion, see Straus J. Produktpatente auf DNA-Sequenzen - Eine aktuelle Herausforderung des Patentrechts. *Gewerblicher Rechtsschutz und Urheberrecht* 2001;10-11:1016-1022. (Product patents on DNA sequences – a current challenge to patent law).

Chapter

6

Conclusions and
recommendations

Conclusions and recommendations

- 6.1 In this paper we have examined issues relating to intellectual property in the context of genetics, particularly those that concern healthcare and research related to healthcare. After considering the ethical and technical issues raised by patenting DNA sequences, we have suggested a number of ways in which the patent system should be modified for the future. We have also made a number of recommendations aimed at ameliorating the deleterious effects of patents that have already been granted.
- 6.2 Despite concerns about the application of the patent system to genetics, we accept the general view that patents have promoted the public interest by encouraging the development of new medicines and vaccines. Both to do justice to the achievements of inventors and because we recognise the importance of stimulating innovation, particularly in the pharmaceutical sector, **we conclude that exclusive rights awarded for a limited period are, in the main, defensible and that the patent system has in general worked to the benefit of people. Nonetheless, we consider that in the particular case of patents that assert property rights over DNA, consideration should be given to whether the balance between public and private interests has been fairly struck (paragraph 2.10).**
- 6.3 We note that in most countries, patent litigation is very expensive and slow. We welcome the efforts of patent offices to improve the efficiency of the various methods for challenging patents (paragraph 2.21).

Are DNA sequences eligible for patenting?

- 6.4 We have considered the question of whether DNA sequences should be eligible for patenting. Even though we think that the judgement that isolated DNA sequences are eligible for patenting is based on a questionable extrapolation to the case of genetic information from the case of the isolation of chemical compounds, we accept that a limited number of the early patents granted on that basis need not now be called into question, in view of the inventiveness required to isolate the DNA sequences. Since the early days of the pioneering experiments using positional cloning techniques, patents have been filed on many DNA sequences which were mass-produced by a mixture of computational and cloning techniques. Even if it can be convincingly argued that these sequences were eligible for patenting, the patents should be examined in the light of the criteria for inventiveness and utility. We note that as techniques have advanced, and in particular as the use of computers to identify genes has become more widespread, the eligibility of DNA sequences for patenting should have diminished (paragraphs 3.22 – 3.25).

Do DNA sequences meet the legal criteria for patenting?

- 6.5 With regard to the legal criteria for assessing patents with claims to DNA sequences, while we accept that the test of novelty can be met, the tests of inventiveness and utility are more problematic. In the case of inventiveness, we hold that as the use of computational databases becomes the standard way of identifying genes, it is difficult to see how this criterion can be fulfilled. Currently, the USPTO and the EPO differ in their application of the criterion. We take the view that the approach of the EPO, which sets a higher threshold for inventiveness, is appropriate (paragraphs 3.30 – 3.34). **We agree that rights asserted over DNA sequences that have been identified and characterised only by *in silico* analysis of**

the DNA sequence and comparisons with other identified sequences should not be allowed, on the grounds of lack of inventiveness (paragraph 5.11). In the case of utility, we argue that the standard of credibility required for a claimed utility needs to be set higher than the mere theoretical possibility of this utility; some positive evidence that the DNA sequence has the claimed utility should be required. Furthermore, the utility in question should be more than a biological function. Even if the biological function ascribed is correct, it is only a description of a fact of nature, and not a practical utility in the usual sense applied to an invented product (paragraphs 3.35 – 3.37).

- 6.6 **In light of these conclusions, we conclude that in the future, the granting of patents that assert rights over DNA sequences should become the exception rather than the norm.** However, since there are various ways in which DNA sequences can be claimed in patent applications, a generalised consideration would generate a superficial and unsatisfactory analysis. Although many patents will assert rights over more than one way of using a DNA sequence, we distinguish four applications of DNA sequences in relation to patent claims: for use in diagnostic tests, as research tools, in gene therapy, and in the production of therapeutic proteins. We consider each of these in turn.

Diagnostic testing

- 6.7 The identification of DNA sequences that are significantly associated with a disease can provide the basis for a diagnostic test. We take the view that the description of an association between a gene and a disease amounts to little more than a discovery. However, in general, the law in most countries has been generous in effectively allowing the applications of discoveries to be regarded as inventions provided that they are useful. We argue that allowing property rights to be asserted over all uses, or even all diagnostic uses, of DNA sequences in relation to diagnostic tests gives inventors too great a monopoly in the light of the contribution and inventiveness of their product, may hamper innovation and may not, in fact, satisfy the legal criteria for patenting. We think it likely that, if left unchanged, the patent system as it is currently applied to DNA sequences in the case of diagnostic tests will have a deleterious effect on the development and use of such tests. **We recommend that the criteria already in place within existing patent systems for the granting of patents, particularly the criterion of inventiveness, be stringently applied to applications for product patents which assert, inter alia, rights over DNA sequences for use in diagnosis. We recommend that the European Patent Office (EPO), the United States Patent and Trademark Office (USPTO) and the Japan Patent Office (JPO) together examine ways in which this may be achieved (paragraph 5.22).** If this recommendation were to be implemented, we expect that the granting of product patents which assert rights over DNA sequences for use in diagnosis would become the rare exception, rather than the norm. Where thresholds for inventiveness are low, as for example in the US, additional mechanisms may be needed. **We recommend, accordingly, that the USPTO and US lawmakers give consideration to whether patent laws need to be amended for this purpose (paragraph 5.22).**
- 6.8 One of the main concerns about asserting rights over a DNA sequence in a product patent is that the patent owner has exclusive rights to all subsequent uses of that sequence. One option that is often suggested as a way to avoid the deleterious effects that may arise as a result, is to limit patents on diagnostic tests based on DNA sequences to use patents, that is, patents which do not assert rights over the DNA sequence itself. If a use patent could be defined so that the owner of the patent is entitled to rights only to the use of the DNA sequence for his specific diagnostic test for a particular disease, and not *all* diagnostic tests

for that disease involving the use of the sequence, this could, on the one hand, provide sufficient incentive for the company to develop the test, and on the other, result in the development and marketing of a number of different tests for the same gene. **We conclude that the protection by use patents of specific diagnostic tests which are based on DNA sequences could provide an effective means of rewarding the inventor while providing an incentive for others to develop alternative tests (paragraph 5.24).**

- 6.9 Patents have already been granted on diagnostic tests that are based on genetic information. We do not support a wholesale and indiscriminate use of compulsory licensing. **Rather, in those specific cases in which the enjoyment of exclusive rights to the diagnostic use of a DNA sequence is not in the public interest, we recommend that those seeking to use the diagnostic tool or develop an alternative should seek a compulsory licence from the relevant authorities if they are refused a licence from the owner of those rights on reasonable terms, and we encourage the authorities to grant such a licence (paragraph 5.29).** We also note the suggestion made by the Organisation for Economic Co-operation and Development (OECD) of a 'clearing house' to ease the obtaining of licences for 'genetic inventions' by commercial laboratories.¹ We suggest that this concept, which might reduce transaction costs, should be explored further (paragraph 5.29).

Research tools

- 6.10 The identification of a gene may belong to the broad category of scientific findings which have no immediate commercial use in themselves but which have been dubbed 'research tools' since they can, like any other scientific information, guide the design of future research. We take the view that the exercise of a monopoly over what are now essentially discoveries of genetic information, accessible by routine methods is, in principle, highly undesirable. We consider that the development of a culture among those who carry out scientific research, whereby claims are made to naturally-occurring material which can be isolated by routine procedures and to which a weakly demonstrated or hypothetical utility may be ascribed to secure some possible future value, if endorsed by the patent offices, amounts to a misapplication of the patent system.
- 6.11 **We consider, therefore, that in general, the granting of patents which assert rights over DNA sequences as research tools should be discouraged (paragraph 5.41).** We take the view that the best way to discourage the award of such patents is by a stringent application of the criteria for patenting, particularly that of utility. **We therefore welcome the recent Utility Guidelines for DNA sequences introduced by the United States Patent and Trademark Office (USPTO), which have, in effect, been endorsed by the European Patent Office (EPO) (paragraph 5.41).**² We suggest that there must be some evidence for the specific and substantial utility claimed in the patent application in order for it to be credible. We consider that the introduction of the Guidelines should go some way to mitigate the tendency of some patent offices to allow rights in relation to DNA sequences to be asserted when any demonstration of utility is, at best, weak. However, it is not yet certain whether they will prove to be sufficient: they have only been in operation for 18 months. **We recommend, therefore, that the United States Patent and**

¹ Organisation for Economic Co-operation and Development. Short summary report of the workshop on Genetic inventions, Intellectual property rights and licensing practices, Berlin, Germany, 24-25 January 2002. Available at <http://www.oecd.org/pdf/M00031000/M00031448.pdf>

² USPTO Utility Examination Guidelines Fed. Reg. 66: 1093. 5 Jan 2001. <http://www.uspto.gov/web/offices/com/sol/notices/utilexmguide.pdf> (20 May 2002).

Trademark Office (USPTO), the European Patent Office (EPO) and the Japan Patent Office (JPO) should monitor the impact of the Guidelines on the examination of patents to ensure that the criterion for utility is rigorously applied so that the grant of a patent more properly reflects the inventor's contribution. If this proves not to be the case, the Guidelines should be reviewed and strengthened to achieve this purpose (paragraph 5.41). Taking further corrective action (if it is needed) cannot be allowed to wait unduly long. As we observed in the case of DNA sequences as they are used in diagnosis (paragraph 5.29), we expect that if this recommendation is implemented, the result will be that patents which assert rights over DNA sequences for use in research will become the rare exception rather than the norm.

- 6.12 If rights in relation to a partial DNA sequence or EST are asserted in a patent, it is possible that the patent will also extend to the full DNA sequence, even though the full sequence may be isolated by someone else without using the EST in question. There is wide agreement that patent protection of partial DNA sequences such as ESTs should not be granted in broad terms. **We recommend that when rights are asserted in terms intended to cover all sequences that contain the EST that is the subject of the original patent, no patent should be granted (paragraph 5.38).** We also endorse the serious concerns expressed by the Human Genome Organisation (HUGO) about the possible deleterious effect on the further progress of genetic research and the successful exploitation of its results, should broad claims within patents of the so-called 'having' and 'comprising' type, be issued for ESTs. We endorse the call of HUGO to patent offices not to issue patents on ESTs without having found solutions to the problem of dependent patents (paragraph 5.38).³ (A dependent patent is one whose exploitation would encroach upon the exploitation of an earlier patent.)

Licensing DNA sequences for research

- 6.13 Many organisations, particularly universities and biotechnology companies, have already been granted patents claiming DNA sequences which have a primary use as research tools. Such organisations are often not well placed to undertake extensive product development and distribution and will often seek to realise the value of their patents through licensing. Under these and other circumstances, the risk arises that an important patent may be licensed exclusively. The resulting exclusivity may not be in the public interest: it may discourage others from working in an area which would profit from a variety of approaches or solutions. **We recommend that those public institutions which already have been awarded patents that assert rights over DNA sequences as research tools be strongly encouraged not to licence them exclusively to one or a limited number of licencees, even when, by not doing so, they may suffer some loss of revenue in the short term. We also recommend that, wherever possible, the private sector should consider non-exclusive licensing for those DNA sequences which are used in research (paragraph 5.42).**

The research exemption

- 6.14 Many researchers want to make use of patented DNA sequences in research when there is no obvious prospect of commercial development arising from that use. This situation will arise in the context of most academic research, as well as some research in industry. Research may be undertaken on inventions which have been patented, including DNA sequences.

³ HUGO. HUGO Statement on patenting of DNA sequences - In particular response to the European Biotechnology Directive. London: HUGO; 2000.

This is generally referred to as the 'research exemption'. Most patent systems have some form of exemption to enable research to be carried out on a patented invention provided it is not intended to produce commercial benefit, so as to ensure that innovative research is not stifled. **We recommend that the 'research exemption' is given a statutory basis in the US and clarified in Europe by policy-makers as a matter of urgency (paragraph 5.45). We further recommend that companies work together to extend the concept of the 'research exemption' throughout industry for DNA sequences which appear in patents and which have a use in research (paragraph 5.45).**

Gene therapy

6.15 Gene therapy aims to replace a faulty gene with a normal gene by introducing it into the body. **We consider that once a gene which is associated with a disease is identified, the use of the relevant DNA sequences in gene replacement therapy, to alleviate the effects of mutations in that gene, is obvious (particularly when such use is claimed on a purely speculative basis). Therefore, we recommend that protection by product patents should seldom be permissible (paragraph 5.49).** We can imagine other forms of gene therapy, where some innovation more complex than simply replacing a damaged gene is involved, which may constitute an inventive step. Certainly, some kind of incentive in the form of patent protection is needed to encourage the development of valid and effective gene therapy. It is a difficult area of technology which requires investment. **We believe that patent protection should be concentrated on developing safe and effective methods of appropriate gene delivery (paragraph 5.49).** This is where the real inventiveness and investment will be required, rather than in simply defining the sequence of the genes to be used in treatment.

Therapeutic proteins

6.16 Therapeutic proteins are proteins produced directly from DNA sequences (in other words, gene products) that have been developed into medicines. We conclude that patents for therapeutic proteins which include the assertion of rights over the relevant DNA sequence are justified (paragraph 5.55). **However, we take the view that while rights asserted over DNA sequences which are used to make new medicines based on therapeutic proteins are generally acceptable, they should be narrowly defined. By this we mean that the rights to the DNA sequence should extend only to the protein described (paragraph 5.56).**

Limiting the scope of product patents in relation to DNA sequences

6.17 The law in many countries, including the US and Europe, has tended to be generous in granting patents which assert rights over DNA sequences. Furthermore, the effects of many of these patents are extensive, because inventors who assert such rights obtain protection on all uses of the DNA and, sometimes, also the proteins which the DNA produces. It is a feature of DNA that one gene will often generate more than one product, for example, different proteins. Consequently, finding novel uses for DNA sequences will be a relatively common event. This is not generally the case in other areas of patenting. The effect of the recommendations which we have made so far in this Paper would be to reduce substantially the number of patents that assert rights over DNA sequences. We consider that if they are granted, there is a strong case to be made for limiting the scope of such patents. If our recommendations are not adopted, then it would be that much more important to develop a mechanism which would limit the scope of product patents. **We recommend, therefore, that the United States Patent and Trademark Office (USPTO), the European Patent**

Office (EPO), the Japan Patent Office (JPO) and other relevant bodies give consideration to the concept of limiting the scope of product patents that assert rights over naturally-occurring DNA sequences to the uses referred to in the patent claims, where the grounds for inventiveness concern the use of the sequence only, and not the derivation or elucidation of the sequence itself (paragraph 5.62).

Scrutiny of patent applications from the perspective of ethics

6.18 There are some inventions that meet the necessary legal criteria for patentability which are excluded from patenting under various international agreements. We note that the scrutiny of patent applications by reference to their being contrary to morality or '*ordre public*' requires expertise in areas that may not be represented in patent offices. These areas include moral philosophy, environmental ethics and public policy. **We recommend that the European Patent Office (EPO) should consider producing further guidance which clarifies the principles set out in Article 53(a) of the European Patent Convention (EPC) concerning patents that are contrary to morality or '*ordre public*'. We recommend that the EPO seek general guidance from the European Group on Ethics (EGE) (paragraph 3.48).**

Appendices

Appendix 1: How patents are granted

The process of filing patents

(a) The European Patent Office (EPO)

Applications for patents in European countries may be filed either with the EPO in Munich, The Hague or Berlin, or with national patent offices. The application is published 18 months after the date on which the European or national first application was filed (priority date). The search report, a list of all published items relevant to the subject of the invention¹, is published either with the application or later on. Applicants then have six months to decide whether or not to pursue their application by requesting substantive examination.

(b) The United States Patent and Trademark Office (USPTO)

US patent applications are filed at the USPTO in Washington. Until November 2000, patent applications were not published. Only if a patent was granted would publication then take place. The US now has a similar system to the rest of the world and patent applications are now published after 18 months provided they are also filed internationally.

The process of examining patents

(a) The EPO

The examination is carried out by the Examining Divisions of the EPO, which is responsible for the examination of each European patent application. On average it takes 44 months to obtain a patent through the EPO. Patent Examiners are primarily involved with undertaking documentary searches (literature searches, including patent literature) and examining patent applications. Conduct of a substantive examination of the application involves initiating a written dialogue with the applicant with a view to transforming the patent application into a patent, subject to satisfaction of the criteria for patenting, laid down in the EPC. If these are not met, a refusal or rejection of the patent application will result.

The process of searching and examining one patent application takes several days. There are three main phases of work, as explained below. Search and examination procedures are normally separate, but under a relatively new procedure can be combined if the applicant so requests.

Preparation

This stage involves the determination of whether the application has been correctly allocated to the Patent Examiner's broad, technical field of expertise and the subsequent re-allocation of the applicant if necessary.

Search procedure

This phase has several components:

- Study of the patent application
- Classification of the patent application
- Definition of the search strategy
- Implementation of the search strategy

¹ The search report is issued by the patent examiners in the Search Divisions of the EPO and comprises both patent and non-patent literature. The purpose of the search report is to check the novelty of the patent application.

- Evaluation of the documents found in the search process
- Production and issuance of a search report

Examination procedure

An examining division comprises three members. Correspondence takes place between the applicant and the examiner to resolve any objections raised by the application. A proposal to grant a patent ('notice of allowance') is produced when objections have been successfully overcome. Correspondence between the applicant and examiner continues until a patent is granted (which occurs in most cases) or an application is refused (where objections have not been successfully overcome or an application is abandoned). Where applications are refused, a reasoned decision, open to appeal, is written.

The applicant also has to perform various formalities (paying fees, filing translations, etc.) before the patent is published in the form as granted.

(b) The USPTO

The role of a Patent Examiner at the USPTO is very similar to the EPO in its key components, which are to:

- review patent applications to assess if they comply with basic format and legal rules;
- determine the scope of the protection claimed by the inventor;
- carry out a literature search (including the patent literature) and the substantive examination of the application, at the same time (the search and examination procedures are a single step, unlike in the EPO, where they are normally separate);
- issue an official letter (referred to as an 'action'), rejecting various claims and objecting to various informalities; occasionally, an application may proceed straight to allowance. The applicant is given a short time in which to respond, during which he can amend the claims. If he still fails to satisfy the examiner, the next official letter is a final rejection. This is not as final as it sounds, as negotiation between applicant and examiner can continue and if this does not lead to allowance, the applicant can appeal to the Board of Appeals of the USPTO. The decision of the Board of Appeals is further appealable to a court.
- a key feature of US patent law is the requirement for a patent applicant to tell the USPTO of any prior art or other materials which might affect the application. If he fails to do this, with deliberate intent, the application is considered not to have been made in good faith. This can lead to the patent being declared invalid by a court. It is therefore normal for patent applicants in the US to file an Information Disclosure Statement, listing all relevant prior art known to the inventor or his patent attorney, even if some of it is of only marginal relevance.²

Patent applications took an average period of 25 months to grant in 1999. The key point of reference here is the *Manual of Patent Examining Procedure*. Like the EPO, the USPTO has a number of examining groups with jurisdiction over certain assigned fields of technology. Each group is headed by a group director. Examiners also deal with applications that claim the same invention and initiation of proceedings known as interferences to determine who was the first inventor. The interference procedure is long and complex and is handled by the Board of Appeals.

² There is an obligation for the patent applicant to disclose what is known, but no obligation to search.

Appendix 2: Historical bibliography of relevant laws, regulations, guidance and legal cases

International

1883:

Paris Convention for the Protection of Industrial Property

An international treaty adhered to by about 110 countries, which helps those who wish to obtain patent protection in more than one country. Someone, who has filed a patent application in any country that is a member to the Paris Convention can, within one year after that filing, file patent applications in other countries, claiming the filing date of the first application as the effective filing date of the later applications.

1970:

Patent Co-operation Treaty (PCT)

The PCT streamlines the first two steps of the various national procedures for obtaining patents. Using the PCT an applicant needs only to file one single patent application in which he indicates all the countries in which he wants to have patent protection. It is administered by the World Intellectual Property Organisation (WIPO).

1994:

TRIPS (Agreement on Trade-related Aspects of Intellectual Property Rights)

For the first time, this is an agreement that contains international mandatory standards as to which subject matter is eligible for patent protection, as well as in respect of the contents, limits and the term of protection. It does not refer specifically to genes. The TRIPS Agreement applies to all 144 WTO member states.

Article 27: Patentable Subject Matter

1. Subject to the provisions of paragraphs 2 and 3, patents shall be available for any inventions, whether products or processes, in all fields of technology, provided that they are new, involve an inventive step and are capable of industrial application. Subject to paragraph 4 of Article 65, paragraph 8 of Article 70 and paragraph 3 of this Article, patents shall be available and patent rights enjoyable without discrimination as to the place of invention, the field of technology and whether products are imported or locally produced.
2. Members may exclude from patentability, inventions, the prevention within their territory of the commercial exploitation of which is necessary to protect *ordre public* or morality, including to protect human, animal or plant life or health or to avoid serious prejudice to the environment, provided that such exclusion is not made merely because the exploitation is prohibited by their law.
3. Members may also exclude from patentability:
 - (a) diagnostic, therapeutic and surgical methods for the treatment of humans or animals;
 - (b) plants and animals other than micro-organisms, and essentially biological processes for the production of plants or animals other than non-biological and microbiological processes. However, Members shall provide for the protection of plant varieties either by patents or by an effective sui generis system or by any combination thereof.

http://www.wto.org/english/tratop_e/trips_e/trips_e.htm (20 May 2002)

1995:

HUGO (Human Genome Organisation) Statement on the Patenting of DNA Sequences

'HUGO is worried that the patenting of partial and uncharacterised cDNA sequences will reward those who make routine discoveries but penalise those who determine biological function or application. Such an outcome would impede the development of diagnostics and therapeutics, which is clearly not in the public interest. HUGO is also dedicated to the early release of genome information, thus accelerating widespread investigation of functional aspects of genes.'

Full statement at: <http://www.hugo-international.org/hugo/patent.htm> (20 May 2002)

HUGO is an international organisation under the direction of an international Council made up of 18 members, from around the world.

1996:

International Strategy Meeting on Human Genome Sequencing, Bermuda

Scientists from genome centres in the UK, the USA, France, Germany, Australia and Japan agree to two principles. First, they pledge to share the results of sequencing 'as soon as possible,' releasing all stretches of DNA longer than 1000 units. Second, they pledge to submit these data within 24 hours to the public database known as GenBank, meaning that anyone can access these data without cost. The goal, according to a memo issued at the time, is to 'prevent ... centers from establishing a privileged position in the exploitation and control of human sequence information.' The Bermuda policy replaces a 1992 US understanding that such data should be made public within 6 months. A summary of the principles agreed at the meeting is available at <http://www.hugo-international.org/hugo/bermuda.htm> (20 May 2002)

1997:

UNESCO Universal Declaration on the Human Genome and Human Rights

The first universal instrument in the field of biology. It aims to strike a balance between safeguarding respect for human rights and fundamental freedoms, and the need to ensure freedom of research. It recognises that 'research on the human genome and the resulting applications open up vast prospects for progress in improving the health of individuals and of humankind as a whole', but emphasises that 'such research should fully respect human dignity, freedom and human rights, as well as the prohibition of all forms of discrimination based on genetic characteristics'.

See http://www.unesco.org/human_rights/hrbc.htm (20 May 2002).

UNESCO currently has 188 member states and 6 associate members.

1997:

HUGO Statement on Patenting Issues Related to Early Release of Raw Sequence Data

This statement reaffirms that 'HUGO does not oppose patenting of useful benefits derived from genetic information, but does explicitly oppose the patenting of short sequences from randomly isolated portions of genes encoding proteins of uncertain functions'. It calls upon law makers to enter into negotiations aimed at reaching an agreement on the introduction of a 'grace period' (as in US law) so to put all participants in the international network on an equal footing.

Full statement available at <http://www.gene.ucl.ac.uk/hugo/ip1997.htm> (20 May 2002)

1999-2000:

World Intellectual Property Organisation (WIPO) Working Group

WIPO brings together a number of experts in the field of biotechnology and intellectual property rights in a Working Group which aims to:

- examine practices related to the protection of biotechnology inventions under patent and plant variety protection systems of WIPO Member States
- review application of certain legal standards in an early stage and certain other biotechnology inventions under patents
- examine legal regimes and university/government practices related to the use of patents to create technology-based collaboration with the private sector and to evaluate the relative success of different models for technology transfer
- assess modalities for technology commercialisation involving biological resources, and prepare studies that may facilitate discussions related to collaboration agreements for conducting R&D of naturally occurring biological materials
- evaluate issues related to the establishment of a multilateral system for the deposit and use of machine-readable nucleotide and amino acid sequence information
- evaluate means for recording ownership interest in inventions arising out of private- public collaborative research and similar projects

Details may be found at <http://europa.eu.int/comm/trade/pdf/biotech.pdf> (20 May 2002). WIPO has 179 member states.

2000:

Joint statement by the UK Prime Minister and the US President Clinton

The statement aims to ensure that discoveries about the human genome are used to advance human health.

Full text at <http://www.patent.gov.uk/about/ippd/notices/genome.htm> (20 May 2002)

2000:

HUGO Statement on Patenting of DNA sequences – In Particular Response to the European Biotechnology Directive

HUGO reiterates that it has repeatedly observed that ESTs constitute research tools and that it opposes the patenting of short sequences from randomly isolated portions of genes. It also maintains that SNPs, as a rule, cannot meet the requirement of inventiveness (non-obviousness). Full statement to be found at <http://www.hugo-international.org/hugo/patent2000.html> (20 May 2002)

Europe¹

1949:

UK Patent Act

The act is effectively spent. Under it and its predecessors, a patent could only be granted for a 'manner of new manufacture'.

1963:

Convention on the Unification of Certain Points of Substantive Law on Patents for Invention ('The Strasbourg Convention')

The Convention is an early attempt to unify the conditions required in order that a patent can be granted for an invention in each of the Parties, and to lay down the criteria to be applied by courts in defining the extent of the protection conferred by the patent. It contains the framework of what became much of the substantive patent law of the European Patent Convention (EPC).

¹ All patent cases that have gone to review by the EPO are listed on the EPC website available at: <http://www.european-patent-office.org>

For example Article 2 is the forerunner of Article 53 EPC:

Article 2

The Contracting States shall not be bound to provide for the grant of patents in respect of:

- a) inventions the publication or exploitation of which would be contrary to *ordre public* or morality, provided that the exploitation shall not be deemed to be so contrary merely because it is prohibited by a law or regulation;
- b) plant or animal varieties or essentially biological processes for the production of plants or animals; this provision does not apply to microbiological processes or the products thereof.

1973:

European Patent Convention (EPC)

Article 52

- 1) European patents shall be granted for any inventions which are susceptible of industrial application, which are new and which involve an inventive step.
- 2) The following in particular shall not be regarded as inventions within the meaning of paragraph 1:
 - (a) discoveries, scientific theories and mathematical methods;
 - (b) aesthetic creations;
 - (c) schemes, rules and methods for performing mental acts, playing games or doing business, and programs for computers;
 - (d) presentations of information.
 - (e) The provisions of paragraph 2 shall exclude patentability of the subject-matter or activities referred to in that provision only to the extent to which a European patent application or European patent relates to such subject-matter or activities as such.
- 3) Methods for treatment of the human or animal body by surgery or therapy and diagnostic methods practised on the human or animal body shall not be regarded as inventions which are susceptible of industrial application within the meaning of paragraph 1. This provision shall not apply to products, in particular substances or compositions, for use in any of these methods.

Article 53: European patents shall not be granted in respect of:

- a) inventions the publication or exploitation of which would be contrary to '*ordre public*' or morality, provided that the exploitation shall not be deemed to be so contrary merely because it is prohibited by law or regulation in some or all of the Contracting States;
 - b) plant or animal varieties or essentially biological processes for the production of plants or animals; this provision does not apply to microbiological processes or the products thereof.
- <http://www.european-patent-office.org/legal/epc/e/contents.html> (20 May 2002).

1978:

European Patent Office (EPO) receives its first applications.

1987:

Genentech's Patent [1987] RPC 553

First patents containing claims to a DNA sequence (on tissue plasminogen activator, t-PA) to reach the UK High Court (Patents Court): principal claims held invalid.

1989:

Genentech's Patent [1989] RPC 147 (CA)

UK Court of Appeal confirms invalidity of Genentech's t-PA patent.

1992:

EPO grant a patent (EP-B-0169672) for the Harvard oncomouse

The first transgenic animal for which a patent is granted under the EPC. The patent is challenged on various grounds, including the 'contrary to morality' clause. After protracted proceedings, the EPO Opposition Division decides in an appealable decision dated November 2001 that the patent must be limited to transgenic rodents containing an additional cancer gene, but that it is not contrary to morality.

1996:

Chiron v Murex 1996 FSR 153 [1996] RPC 535

Hepatitis C patent upheld by UK Court of Appeal. (See chapter 4, case study 3)

1996:

Biogen Inc v Medeva plc 1 November 1996

The issue of the scope of a patent claim reaches the House of Lords, when a claim to an invention of 'a recombinant DNA molecule ... coding for a polypeptide ... displaying hepatitis B virus [HBV] antigen specificity' was found to be too broad.

1998:

European Directive 98/44/EC

The Directive sets out what is and what is not excluded from eligibility for patenting. It states that:

Article 3.1: 'Inventions which are new, involve an inventive step and are susceptible of industrial application are patentable even if they concern a product consisting of or containing biological material ('biological material' means any material containing genetic information and capable of reproducing itself or being reproduced in a biological system). Biological material which is isolated from its natural environment or produced by means of a technical process may be the subject of an invention.

Article 4.1: Plant and animal varieties and essentially biological processes for the production of plants or animals, including crossing or selection, are not patentable.

Article 5.1: The human body and the simple discovery of one of its elements, including the sequence or partial sequence of a gene, cannot constitute patentable inventions. However, an element isolated from the human body or otherwise produced by means of a technical process, including the sequence or partial sequence of a gene, may constitute a patentable invention.

Article 6.2: The following inventions include those that are unpatentable where their exploitation would be contrary to *ordre public* or morality:

- processes for cloning human beings;
- processes for modifying the germ-line genetic identity of human beings;
- uses of human embryos for industrial or commercial purposes;
- processes for modifying the genetic identity of animals which are likely to cause them suffering without any substantial medical benefit to man or animal, and also animals resulting from such processes.'

http://europa.eu.int/smartapi/cgi/sga_doc?smartapi!celexapi!prod!CELEXnumdoc&lg=EN&numdoc=31998L0044&model=guichett (20 May 2002)

To date, five Member States have fully implemented the Directive: Denmark, Finland, Greece,

Ireland and the UK. Various countries have challenged the Directive and are still in discussion regarding its implementation. The EPO, although not formally bound by the Directive, has amended its rules in compliance with it.

1999:

Case G1/98 (Transgenic Plant/NOVARTIS II) heard by the Enlarged Board of Appeal

The Swiss company Novartis applied for a patent for a process for creating transgenic plants which contain genes for pathogen-resistance, an application that included claims to the plants produced by this process. This was initially rejected on the grounds that it was excluded from eligibility for patenting under Article 53(b) of the European Patent Convention, following the earlier decision T356/93. The Enlarged Board of Appeal overturns the earlier judgement. It holds that a claim in which specific plant varieties are not individually claimed is not excluded from eligibility for patenting under Article 53(b) EPC, even though it may embrace plant varieties. This is a landmark decision as the Enlarged Board of Appeal accepts that plants themselves can be patented, rather than merely methods of producing them. The decision is criticised by environmental organisations.

2000:

EPC Revision Conference

Article 53 EPC is amended to read as follows:

Article 53: Exceptions to patentability

European Patents shall not be granted in respect of:

- a) inventions the commercial exploitation of which would be contrary to *'ordre public'* or morality, provided that such exploitation shall not be deemed to be so contrary merely because it is prohibited by law or regulation in some or all of the Contracting States;
- c) methods for treatment of the human or animal body by surgery or therapy and diagnostic methods practised on the human or animal body; this provision shall not apply to the products, in particular substances or compositions, for use in any of these methods.

Full details of the Act Revising the Convention on the Grant of European Patents may be found at http://www.european-patent-office.org/epo/dipl_conf/pdf/em00003a.pdf (20 May 2002). The agreed amendments have not yet come into force.

2001:

Doha Agreement

Declaration on the TRIPS Agreement and public health is adopted at the fourth WTO Ministerial Conference in Doha, Qatar.

2001:

Patent 0 630 405

A patent on a 'novel V28 seven transmembrane receptor' (which includes a DNA sequence) was granted to ICOS Corporation in 1998. It was opposed by SmithKline Beecham and Duphar International Research. The patent is revoked in 2001. The EPO holds that since the purified and isolated DNA sequence does not exist in nature, it is not a discovery and is therefore patentable. However, they find that it fails to meet the criteria of inventive step and industrial application. Recital 23 of the 1998 EC Directive states that 'a mere DNA sequence without indication of a function does not contain any technical information and is therefore not a patentable invention.' The EPO decision states that indications of function are required to be more than speculative, and that indications of function which are not substantial, specific and credible are not patentable because they lack technical character. An appeal is lodged but has not yet been decided upon.

United States

1793:

Patent Act

An early and almost unchanged definition of patentable subject matter: 'any new and useful art, machine, manufacture or composition of matter and any new and useful improvement on any art, machine, manufacture or composition of matter'.²

1952:

US Patent Act

35 U.S.C., one of four principal statutory authorities under which USPTO programmes are conducted, is derived from this Act. 35 U.S.C. contains the basic authorities for administration of patent laws in the US. The two key changes made to the 1793 law are the inclusion of the criterion for novelty and a definition of infringement.

1958:

Merck & Co. v. Olin Mathieson Chemical Corporation 253 F.2d 156, 161, 163

Olin Mathieson challenges Merck's patent on isolated vitamin B12 arguing that Merck had not invented Vitamin B12 but only purified it. The court holds that the product claims to a bacterially produced vitamin B12 protein, although known in nature, are patentable because the claims recite a specific purity limitation. The court states 'There is nothing in the language of the [1952] Act which precludes the issuance of a patent upon a 'product of nature' when it is a 'new and useful composition of matter'. . . All of the tangible things . . . for which patent protection is granted are products of nature in the sense that nature provides the source materials.' The court further notes that '[t]he fact . . . that a new and useful product is the result of processes of extraction, concentration and purification of natural materials does not defeat its patentability.'

1980:

The possibility of re-examination of patents is introduced

1980:

Diamond v. Chakrabarty 447 US 303

In 1972 Chakrabarty filed a patent application for a genetically engineered bacterium that breaks down multiple components in crude oil – a property possessed by no naturally-occurring bacterium. His application was rejected by the USPTO on two grounds: (1) that microorganisms are 'products of nature' and (2) that as living things they are not patentable subject matter. However, the Supreme Court holds that the new bacteria are not 'products of nature', having been genetically modified, and that the fact that microorganisms are alive is without legal significance for purposes of the patent law.

1980:

Bayh-Dole Act

Enables small businesses, universities, and other non-profit federal contractors and grantees to obtain exclusive rights to their inventions.

1981:

Diamond v. Diehr 450 US 175, 185 (1981)

² See 'A Brief History of the Patent Law of the United States' for developments. Ladas and Parry, Intellectual Property Lawyers. www.ladas.com/USPatentHistory.html (20 May 2002)

The Supreme Court holds that patent protection is not available for 'laws of nature, natural phenomena, and abstract ideas.'

1987:

Ex parte Allen 2 USPQ 2d 1425 (Bd. Pat. App. & Interferences 1987)

The Patent Office's Board of Patent Appeals and Interferences rules that oysters which have been artificially treated to alter the number of their chromosomes are properly patentable subject matter under section 101 of the patent statute, 35 USC 101 (1982).

1991:

NIH files a patent application on ESTs

The first patent claim of this type. Although the NIH abandons the application (and other subsequent similar claims) in 1994, there is widespread controversy, increased by ongoing commercial efforts to generate large numbers of ESTs. A widespread view in scientific circles is that EST patents will restrict basic research. However, the patent law community focuses on whether claims to partial gene sequences, without disclosure of actual protein function, meet the statutory requirements for utility and enablement.

<http://www.pst.fraunhofer.de/pla/german/info/news/archiv/10020.htm> (20 May 2002)

1991:

Amgen Inc. v. Chugai Pharmaceutical Co. 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir 1991)

Amgen's patent claimed a purified and isolated DNA sequence encoding human erythropoietin (Epo), Chugai claimed that another inventor, Dr. Fritsch, had conceived earlier a method for obtaining Epo. However, Fritsch had not isolated the gene or identified its structure. The court rules in favour of Amgen on the basis that it is not enough to know how a compound of unknown structure (in this case the Epo gene) might be isolated in order to claim conception; the inventor must actually isolate the gene. This is an important case in that the judgement prevented a company from getting very broad-based claims on all DNA sequences that code for a protein or analogues of that protein.

1993:

In re Bell 991 F2d 781 26 USPQ2d 1529 Fed.Cir. 1993

In this case the patent application included a claim for DNA sequences encoding insulin-like growth factors (hIGF). The PTO reasoned that once a portion of the amino acid sequence is known, the method for isolating DNA sequences encoding a given protein is obvious. The Court of Appeals for the Federal Circuit disagrees, focusing on the structure of a DNA sequence rather than on the method used to obtain the sequence. The Court of Appeals recognises that because of the degeneracy of the genetic code, a vast number of nucleotide sequences that might code for a specific protein exist. Thus, what the applicants had done was not obvious.

1995:

In re Deuel 34 USPQ 2D 1210 Fed. Cir. March 28 1995

The applicants sought a patent for their processes of isolating and manufacturing specific DNA molecules. Their application was rejected on the grounds that DNA sequencing is a standard technique and therefore 'obvious' to the skilled scientist. The applicants appealed and the court's decision is reversed, on the grounds that the general method of isolating DNA molecules is essentially irrelevant to the question of whether or not the specific molecules themselves would have been obvious, as prior art had not disclosed the specified molecules.

1997:

First EST patent granted to Forsyth Dental, Boston

US patent no. 5,656,728 granted for purified DNA sequences encoding all or a portion of an osteoclast-specific or -related gene products and a method for identifying such sequences.

1997:

Speech by Assistant Commissioner of Patents Lawrence J. Goffney

The PTO determines that, at least in 'certain' unspecified circumstances, EST claims, in principle, do comply with the utility and enablement requirements.

<http://www.pst.fraunhofer.de/pla/german/info/news/archiv/10020.htm> (20 May 2002)

1997:

***The Regents of the University of California v. Eli Lilly* 119 F3d 1559**

The University of California (UC) claims that Lilly has infringed its patents in its manufacturing of human insulin. One of these patents is based on the determination of cDNA sequences from rats, but the claims were extended to cover mammalian and human insulin cDNA. The Federal Circuit Court determines that these claims are not sufficient or enabled for human insulin cDNA. 'Describing a method of preparing cDNA or even describing the protein that the cDNA encodes does not necessarily describe the cDNA itself. No sequence information indicating which nucleotides constitute human cDNA appears in the [UC] patent, as appears for rat cDNA ... Accordingly, the specification does not provide a written description of the invention.'

1999:

Incyte granted EST patent (human protein kinase homologues)

2001:

***Amgen, Inc v Hoechst Marion Roussel AG and Transkaryotic Therapies, Inc* 126F Supp. 2d 69 D. Mass. 2001**

Amgen claimed infringement of its patents on Epo, both in relation to its drug, Epogen, a purified version of Epo, and the method of making it. The ruling reaffirms the fact that a patent on a product *per se* will be infringed by a competitor making the same product - no matter what process is used to make that product.

2001:

USPTO publishes revised Utility Guidelines

Revised guidelines clarify the utility requirement for patent claims on genomic and other biotechnological inventions. The new rules demand specific and substantial utility that is credible. 'An excised gene is eligible for a patent as a composition of matter or as an article of manufacture because that DNA molecule does not occur in that isolated form in nature...Synthetic DNA preparations are eligible for patents because their purified state is different from the naturally occurring compound.' Full guidelines as published 5 January 2001 are to be found at:

<http://www.uspto.gov/web/offices/com/sol/notices/utilexmguide.pdf> (20 May 2002)

Glossary

- Amino acid:** Molecules which link together to form *polypeptides* which form *proteins*.
- Antibodies:** *Protein* produced by the immune system in response to a foreign molecule. Antibodies bind to a specific molecule very tightly so can be used as markers.
- Antigen:** A foreign molecule that elicits an antibody response.
- Assignment:** The transfer of *intellectual property* rights from the owner of the rights to another person or organisation.
- Biotechnology:** The use of biological processes to manufacture products.
- Claims:** The definition of the monopoly rights that a *patent* applicant is trying to obtain for the invention. The claims limit the patent owner's monopoly.
- Clone:** A line of cells derived from a single cell and therefore carrying identical *genetic material*. A cloned *gene* is a *gene* that has been *isolated* and replicated.
- Complementary DNA (cDNA):** DNA with a *nucleotide* sequence that is complementary to *RNA* (e.g. the complementary sequence to G-T-A-C is C-A-T-G). Complementary DNA is synthesised from a messenger *RNA* (mRNA) template.
- Composition of matter patent:** Another term, used mainly in the US, for a *product patent*.
- Comprising:** In *patent claims*, comprising means that the *claims* are open-ended. As such, the *claim* is not limited to only what is in the *claim*.
- Dependent patent:** A *patent* on an invention whose exploitation would encroach upon the exploitation of an earlier *patent*. A dependent patent becomes independent with the expiration of an earlier *patent*.
- Diagnostic tests:** Tests used by physicians to make a diagnosis by testing for particular diseases, conditions, or predispositions.
- DNA (deoxyribonucleic acid):** DNA is the biochemical substance that *genetic material* is made of. The DNA in a cell is usually in several long lengths, each of which contains many *genes*.
- Drug target:** A *gene*, or the *protein* it encodes, that plays a role in a disease and is the intended site of drug activity.
- Enhancer:** A *DNA* sequence that increases the rate of *transcription* of a gene even though it may be separated from the gene by several thousand base pairs.
- Erythropoietin (Epo):** A *hormone* produced by the kidney, and to a lesser extent by the liver, that promotes the formation of red blood cells by the bone marrow. The resultant rise in red cells increases the oxygen-carrying capacity of the blood. Epo has been synthetically produced using *recombinant DNA* technology for use as a treatment for people with certain types of anaemia.
- Exon:** The region of *DNA* within a *gene* that codes for a *polypeptide* chain or domain. Usually a *protein* is made up of multiple domains, each coded for by different exons within a single *gene*.
- Expressed sequence tag (EST):** A short section of *complementary DNA* sequence, where location and *nucleotide* sequences are known. ESTs have applications in the discovery of new human *genes*,

mapping of the human genome, and identification of coding regions in *genomic* sequences.

G-CSF (granulocyte colony stimulating factor): A growth factor found in the blood and bone marrow that promotes the production and development of granulocytes (a type of white blood cell). G-CSF is found in tiny amounts in human tissue, but can be manufactured using *recombinant DNA* technology and is available as a drug to treat people with HIV and people recovering from bone marrow transplants.

Gene: A gene is an ordered sequence of *nucleotides* located in a particular position on a particular chromosome that encodes a specific functional product (ie a *protein* or *RNA* molecule).

Gene expression: The process by which information contained in a *gene* is used to produce *proteins* or functional *RNA* molecules. Gene expression has two stages: *transcription* and *translation*.

Genetic engineering: The technology used to genetically manipulate living cells to produce new chemicals or perform new functions.

Genetic material: The material made of *DNA* in each cell of any organism.

Genetic testing: Analysing *DNA* to look for a genetic alteration that may indicate an increased risk for developing a specific disease or disorder, or for the purpose of diagnosis.

Genome: The term genome describes all the *genetic material* of an organism.

Genomics: The study of *genes* and their function.

Homology: Similarity in *gene* or *protein* sequences between individuals of the same species or among different species.

Hormone: A molecule secreted by a cell or tissue in an organism, which has a functional consequence in other cells located remotely.

Human Genome Project: An international collaborative project which determined the sequence of the entire three billion *nucleotides* of the human *genome*.

In silico: The use of computers to simulate, process, or analyse a biological experiment.

Infringe: To make, use or sell a patented item or process within the country covered by the *patent* without permission or *licence* from the patent owner. *Infringement* can occur with or without the accused's knowledge of the *patent*.

Intellectual property: An intangible form of personal property. *Patents*, copyrights, trademarks, service marks, trade names and trade secrets are examples of intellectual property.

Intron: A *DNA* sequence that interrupts the protein-coding sequence of a *gene*. Introns are transcribed into *RNA* but are excised before *translation* into a *protein*.

Inventiveness: One of three legal criteria by which patent applications are assessed. The concept that the invention must involve an inventive step, ie one that would not have been obvious to a person skilled in the art at the time the application for a *patent* was filed (see also *non-obviousness*).

In vitro: Occurring outside the living organism; typically an experiment performed in a test tube or other artificially designed environment.

Isolation: Isolating a *gene* means extracting it from its naturally occurring location in the *genome*.

Licence: A transfer of *patent* rights that does not amount to an *assignment*. A licence, which can

be exclusive or non-exclusive, does not give the licensee the legal title to the *patent*.

Microarray: A microchip containing thousands of *DNA* sequences in an ordered array, which allows simultaneous analysis of thousands of genetic markers or *cDNA* sequences.

Mutation: Any alteration to *DNA* that can potentially result in a change in the function of one or more *genes*. Mutations may be caused by mistakes during cell division, or they may be caused by exposure to DNA-damaging agents in the environment. Mutations can be harmful, beneficial, or have no effect. If they occur in cells that make eggs or sperm, they can be inherited; if mutations occur in other types of cells, they are not inherited. Certain mutations may lead to cancer or other diseases.

Non-obviousness: One of the US criteria by which patents are assessed which requires an invention to involve an insight not obvious to a person knowledgeable about the relevant subject matter (see also *inventiveness and skilled in the art*).

Novelty: One of three legal criteria by which patent applications are assessed. The concept that the *claims* in a patent must be totally new. An invention must have been previously unknown and unavailable to the public when the *patent* is filed.

Nucleotide (nucleotide base): Nucleotides are the subunits from which *DNA* and *RNA* molecules are assembled. A nucleotide is a base molecule (adenine, cytosine, guanine or thymine in *DNA*; adenine, cytosine, guanine or uracil in *RNA*), linked to a sugar molecule and phosphate groups.

Patent Law: Law governing the rights to inventions.

Patent: A legal document providing an exclusive right to the owner for the invention claimed therein.

Patentability: The ability of an invention to satisfy the legal requirements for obtaining a *patent*.

Polymerase chain reaction (PCR): An *in vitro* method for generating unlimited copies of any fragment of *DNA*. PCR exploits the enzymes known as polymerases, which copy *genetic material*. PCR can be used to characterise, analyse, and synthesise any region of *DNA* which lies between two regions of known *sequence*.

Polypeptide: A *protein* or part of a protein made of a chain of *amino acids*.

Prior art: Previously used or published technology that may be referred to in a patent application or examination report.

Probe: A section of cloned *DNA* labelled either radioactively or immunologically, used to isolate a *gene*, *RNA* or a *protein*.

Product patent: A *patent* on a product itself. The term 'product' normally means a chemical or biological entity, substance or composition. A *patent claim* to a product itself covers all uses of that product.

Promoter: A *DNA* sequence to which RNA polymerase (an enzyme which catalyses the synthesis of *RNA* from *DNA*) will bind and begin *transcription*.

Prostate-specific antigen test (PSA test): A blood test that measures prostate-specific antigen (PSA), a protein produced by the prostate gland. A high level of PSA usually indicates a prostate problem (although not necessarily cancer).

Protein: Proteins are biological molecules encoded by an organism's *genome*. Proteins are

essential for all life processes. A protein consists of chains of *amino acid* subunits. The functional action of a protein depends on its three dimensional structure, which is determined by its *amino acid* composition.

Proteome: The total *protein* complement of an organism.

Proteomics: The systematic separation, identification and characterisation of the *proteins* of a whole *genome*.

Purification: In legal terms, purification is the isolation of a naturally-occurring compound from molecules that surround it.

Receptor: A molecular structure within a cell or on the surface that specifically recognises and binds compounds acting as molecular messengers. These molecular messengers may be agonists (drugs or compounds that initiate a physiological or pharmacological response characteristic of the receptor) or antagonists (molecules that inhibit the effect of the agonist). Receptors are important as sites for *drug targets* eg. the CCR5 receptor (see Chapter 4, case study 2).

Recombinant DNA: A combination of *DNA* molecules of different origin that are joined using recombinant DNA technologies. Recombinant DNA technology was developed and patented in the 1970s. It was non-exclusively licensed with low fees.

Research exemption: A doctrine that enables the unlicensed use of a patented invention in pure research with no commercial implications.

Research tools: The full range of resources that scientists use in the laboratory. This may include cell lines, monoclonal *antibodies*, reagents, animal models, growth factors, combinatorial chemistry libraries, drugs and *drug targets*, *clones* and cloning tools, laboratory equipment and machines, databases and computer software.

Reverse transcription: The process by which the messenger *RNA* content of a cell is converted into *DNA*.

RNA (ribonucleic acid): A single stranded nucleic acid molecule comprising a linear chain made from four bases (A,C,G and U). There are three types of RNA: messenger (mRNA), transfer and ribosomal.

Sequencing: Determining the order of *nucleotides* in a *DNA* or *RNA* molecule.

Single nucleotide polymorphism (SNP): *DNA* sequence variation that occurs when a single *nucleotide* (A,T,C,or G) in the *genome* sequence is altered.

Skilled in the art: For an invention for be patentable it must be *non-obvious* to one skilled in the art, ie an ordinary worker with a good knowledge and experience of the subject.

t-PA (tissue plasminogen activator): A thrombolytic or clot-dissolving enzyme that is produced naturally by cells in the walls of blood vessels and catalyses the conversion of plasminogen to plasmin. A preparation of t-PA is produced by *recombinant DNA* technology and is used in the treatment of heart attacks and strokes.

Transcription: The process by which the gene's *DNA* sequence is copied into *RNA*.

Translation: The process by which *RNA* directs the synthesis of a *protein*.

Use patent: A *patent* on the use of a product for a specific purpose; only the specified use is covered.

Utility: One of three legal criterion by which patent applications are assessed which requires that an invention must serve a specific function or purpose.

Glossary of Acronyms

AIDS	Acquired Immune Deficiency Syndrome
DNA	Deoxyribonucleic acid
EGE	European Group on Ethics
EPC	European Patent Convention
Epo	Erythropoietin
EPO	European Patent Office
EST	Expressed Sequence Tag
EU	European Union
G-CSF	Granulocyte Colony Stimulating Factor
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HGS	Human Genome Sciences Inc
HIV	Human Immunodeficiency Virus
HUGO	Human Genome Organisation
ICR	Institute of Cancer Research (UK)
IP	Intellectual Property
IPC	International Patent Classification
IPR	Intellectual Property Rights
JPO	Japan Patent Office
MSP	Merozoite surface protein
MVI	Malaria Vaccine Initiative
NGO	Non-governmental Organisation
NHS	National Health Service (UK)
NIH	National Institutes of Health (US)
PATH	Programme for Appropriate Technology in Health
PCR	Polymerase chain reaction
PCT	Patent Co-operation Treaty
PSA	Prostate-specific antigen
RNA	Ribonucleic acid
SNP	Single Nucleotide Polymorphism
t-PA	Tissue plasminogen activator
TRIPS	Trade-related Aspects of Intellectual Property Rights
TSC	The SNP Consortium
UC	University of California
UNESCO	United Nations Educational, Scientific, and Cultural Organisation
UPOV	Union for the Protection of New Varieties of Plants
USPTO	United States Patent and Trademark Office
WIPO	World Intellectual Property Organisation
WTO	World Trade Organisation



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