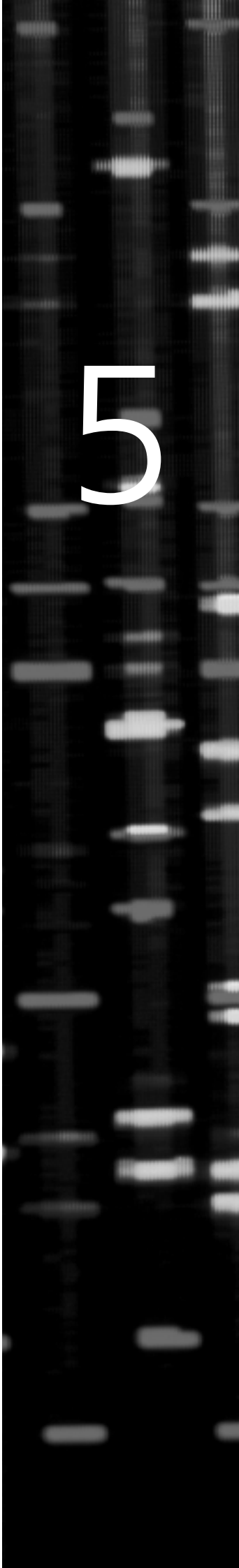
Chapter 5

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, in 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.

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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 genes[9] 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/020319barbaracaufield.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.)

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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 licencee'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.

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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. Secondarily, 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-occuring 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 Rechtsshutz und Urheberrecht 2001;10-11:1016-1022. (Product patents on DNA sequences – a current challenge to patent law).