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Biomedical Patents

In October 2011, the European Court of Justice banned patents for inventions involving stem cells derived from embryos. This case highlighted some of the challenges the patent system faces when assessing biomedical inventions. This POSTnote considers how patent law is applied to biomedical inventions and examines the potential impact on patient access to diagnostic tests and innovation.

Overview

- Biomedical technology presents unique technical and ethical challenges to the patent system.
- Criteria for patentability and its interpretation vary between Europe and the USA.
- Recent litigation in the USA and Europe has questioned the patentability of DNA and the morality of patenting human embryonic stem cells.
- Patents provide an incentive for innovation but restrictive licensing of patents can hinder knowledge transfer. Some of these issues could be addressed by initiatives such as patent pools and patent clearinghouses.
- There is potential for patents to impact on patient access to high quality diagnostic tests on the NHS.

Background

Biomedical technology encompasses stem cell therapies, gene sequencing, diagnostic tests or therapeutic delivery systems. The UK is a leader in this sector with a 31% (£4.6 bn) share of market sales across Europe and an annual turnover increase of ~20% year on year.[1] One driver for innovation in this area is the ability to gain a period of market exclusivity on an invention through patents. These are awarded on a first-to-file basis by agencies such as the European Patent Office (EPO) (Box 1) and the United States Patent and Trademark Office (USPTO). Both apply similar criteria when assessing patentability:

- novelty;
- inventiveness or non-obviousness;
- utility or industrial applicability.

Both the USA and Europe (Box 1) have sought to provide clear guidelines on what is patentable in this field of research. However, the interpretation of patent law can vary as a result of precedent set by judicial bodies. Issues surrounding biomedical patents which provide specific challenges are:

- patentability of DNA and genetic biomarkers;
- patenting of methods and processes;
- requirements for novelty, inventiveness and utility;
- ethics in patent law;
- innovation and patient access to biomedical technology.

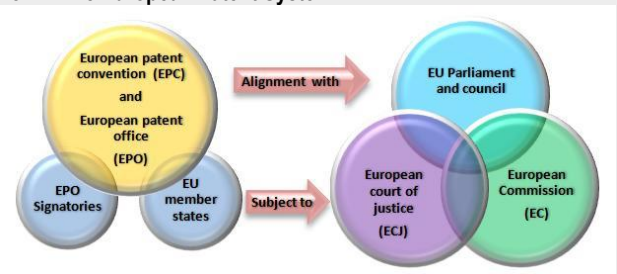
The Patentability of DNA

Attempts to patent human gene sequences have raised significant questions over whether a DNA sequence is an invention or a product of nature. Over time, legislation or case law in Europe and the USA has shaped a consensus that DNA which has been removed from the human body or produced by a technical process (isolated DNA) with a known function is patentable.

Some of the early patents granted on gene sequences included broad, speculative claims to disease areas, diagnostic tests and therapeutic treatments. Patents awarded to Myriad Genetics gave the company a monopoly in the USA on tests for breast cancer susceptibility using the BRCA gene. The scope of the US patents has changed following recent court rulings (Box 2). In Europe, the diagnostic patents awarded to Myriad were significantly narrower in scope than the patents granted in the USA.

This case illustrates that the scope of a patent granted for the same invention can differ between countries. For example, the US patent awarded to Myriad had a very broad scope that gave the patent holder exclusive rights covering uses of the gene in question. This prompted some organisations to adopt a defensive patenting strategy. For example, the BRAF and ErbB2 genes are diagnostic and therapeutic targets for a number of cancers. Patents were

Box 1. The European Patent System



The EPC is a non-EU treaty currently signed by 38 countries including all EU member states. It provides an autonomous legal system for granting patents operated by the EPO. It enables a patent to be granted across all EPO signatories circumventing the need to apply to individual national patent offices. National courts are responsible for enforcing the patents; EU national courts are subject to the ECJ which interprets and enforces approved legislation drafted by the EU. The EPO sits outside EU jurisdiction but has chosen to align itself with the EPC and the EU "Biotech Directive" (see below).

European Unitary Patent for EU member states
Attempts to establish a single European patent system have been underway for the last 50 years. Although the EPO can grant Europe-wide patents, post–grant patents are subject to national legislation. The goal of the unitary patent is to reduce the cost and time it takes to get a patent in Europe by establishing a centralised court system to deal with litigation of European patents. The regulatory draft of the European patent is now in place and the structure of the centralised court is currently under development.

EU "Biotech Directive"[2]
The directive on the legal protection of biotechnological inventions (the "Biotech Directive") was adopted in 1998. Its purpose was to create harmonisation of patent law for biotechnological inventions across Europe and encourage innovation within the field. The following cannot be patented according to the "Biotech Directive":

- plant and animal varieties and biological processes for the production of plants and animals;
- the human body at the various stages of its formation, development or the mere discovery of one of its components;
- processes for cloning human beings, genetic modification of the human germ line (eggs, sperm) and use of human embryos for industrial or commercial purposes; commercial exploitation of such inventions is contrary to *ordre public* or morality;
- genetic modification of animals which could cause suffering without any substantial medical benefit to man or animal and any animals resulting from such processes.

filed by the Wellcome Trust on the polypeptides encoded by these genes and a non-exclusive licensing strategy was adopted. This prevented anyone gaining a commercial monopoly over their use in Europe.

Genetic Biomarker Patents

Over time, the context for patenting DNA has changed. The number of patents claiming gene sequences decreased significantly after the publication of the human genome in 2001. Furthermore, technological advancement and accumulation of case law have meant that it is now more difficult for DNA patent applications to meet the legal requirements for patentability. While many have welcomed this development, concerns are emerging over patenting of fragments of DNA known as genetic biomarkers. These

Box 2. Case Study: Myriad Genetics Gene Patent Litigation

In the USA
The American Civil Liberties Union (ACLU) filed a lawsuit in the USA against Myriad Genetics over patents held by Myriad on the breast cancer (BRCA 1&2) gene sequences and tests which assess genetic susceptibility to breast and ovarian cancer. They argued that the broad nature of Myriad's patents had allowed them to gain an unfair monopoly over BRCA screening in the USA. In 2010, the district court invalidated all of Myriad's BRCA gene patents. Upon appeal to the federal courts, Myriad's gene patents were reinstated but their methods for analysing and comparing BRCA sequences were deemed not patentable subject matter.[3]

In Europe
In Europe, Myriad were granted patents for diagnostic use of the BRCA1 gene sequence but not the gene itself. In 2000, the NHS already offered diagnostic BRCA 1&2 screening and were potentially infringing Myriad's patent.[6] Myriad could have threatened legal action if the NHS did not obtain a licence; a move which would be costly and could lead to inequality in availability of BRCA screening on the NHS. Before negotiations were concluded, the EPO revoked Myriad's BRCA 1 gene patent and on appeal significantly narrowed the scope of their diagnostic patents. This enabled European laboratories to continue offering the BRCA 1 test with less risk of infringing Myriad's patents.[3]

are measureable DNA sequences which can be used to assess the likelihood and extent to which a patient will respond to specific treatments. An increase in the number of patents covering biomarkers has led to concerns over the impact this increase may have on innovation in, and patient access to, diagnostic tests (see page 4).

Methods and Processes

The patentability of methods of medical treatment and diagnostic tests performed directly on the patient differs between the USA and Europe. For example, methods of treatment are allowed under US, but not under EU, legislation. However, diagnostic methods performed on samples after they have been taken from the body fall outside this exclusion. Litigation in the USA has questioned whether diagnostic methods such as those that compare DNA sequences are patentable inventions. In the USA, one test to establish whether such method's can be patented is the "machine or transformation" test. This requires that an invention must be intrinsically linked to a machine or it must transform something into a different state or entity (Box 3).

Novel, Inventive and Useful?

In the USA, patents are granted both for discoveries (except natural phenomena) and inventions. In Europe, discoveries are not patentable although a discovery, together with its technical application, is not excluded from patent protection. In both systems, an invention can be patentable if it:

- has not previously been disclosed to the public (novelty);
- is not obvious to a skilled worker within the field (inventiveness);
- is capable of industrial application or has utility (usefulness).

Some have questioned whether isolated DNA adequately fulfils these criteria. Advances in DNA sequencing mean that isolation of DNA is now a routine, often industrialised process which may no longer be considered inventive.

Box 3. Case Study: Prometheus v. Mayo Collaborative Services
Prometheus holds patents for methods of determining the optimal dosages of two drugs use to treat irritable bowel disorders. Mayo had purchased and used Prometheus's tests but later announced it would use and sell a test it had developed 'in-house'. Prometheus then filed against Mayo for infringement. Mayo argued that Prometheus's patents were invalid as they fail the "machine or transformation" test.[4]

The Findings of the US Courts
- The District court invalidated Prometheus's patents on the grounds that its test merely observed correlations which are a natural phenomenon and therefore not patentable;
- The Federal court overturned the district court ruling, stating that Prometheus's test did have a transformative step and was not just a data gathering exercise;
- The Supreme court upheld the findings of the Federal court stating that the "machine or transformation" test was not the sole test for determining patentability.

However, it is generally accepted that the identification of new DNA sequences fulfils the requirement for novelty. With respect to utility, it is often the case that theoretical applications are sufficient to satisfy this criterion and clinical evidence is not always required to support such claims. These issues have been clarified by a recent UK Supreme Court case (Box 4).

Box 4. Case Study: Eli Lilly v. Human Genome Sciences (HGS)
Eli Lilly filed a case requesting revocation of an HGS patent which describes the DNA and amino acid sequences for neutrokine-α. Neutrokine-α, is involved in regulating inflammatory and immune responses. HGS identified the sequences using computational techniques and listed a number of potential applications for treating or diagnosing a range of diseases. These applications were largely based on theoretical, not experimental, evidence. Eli Lilly alleged that the invention was not patentable as it lacked inventiveness and industrial applicability. Initially the court found in favour of Eli Lilly and revoked the patent. The case was appealed to the UK supreme court which reinstated the patent, and clarified the patent requirements.
- A patent must disclose a practical application and profitable use for the invention.
- Simply identifying a sequence without suggesting a real application is not acceptable. A plausible use or an educated guess for such a use can suffice, and this can be confirmed by later evidence.

Ethics and Patent Law

Biomedical research can result in inventions which are ethically controversial such as human cloning, embryonic stem cells and transgenic animals. In the USA, there are no explicit requirements in patent law to consider the ethical implications of an invention when assessing its patentability. Furthermore, it is generally held that *'anything under the sun that is made by man'* is patentable subject matter.

The Morality Clause in European Patent Law

The EPC excludes from patent rights inventions whose commercial exploitation would be contrary to *ordre public* or morality. The EU "Biotech Directive" provides examples of inventions which should be excluded on this basis. Advances in biomedical technology have placed the ethical assessment of inventions high on the agenda in Europe.

Ethics of Patenting Human Embryonic Stem Cells

Human embryonic stem cells (hES cells) are generally obtained from embryos that are surplus to the requirements of *in vitro* fertilisation programmes. These cells can be cultured in the laboratory as cell lines. hES cell lines do not have the potential to develop in to embryos but are of interest to researchers as they can be transformed into any other type of cell. However, hES cells raise ethical concerns as their isolation usually results in embryo destruction.

In 2008, the Enlarged Board of Appeal within the European Patent Office determined that any patent application concerning an invention which necessitates the destruction of an embryo will be refused. EPO practice following the decision was to accept patent applications involving hES cells if the invention could be carried out using cells derived from existing cell lines. This position is now in doubt after a recent ruling by the European Court of Justice (Box 5).

Box 5. Case Study: Brüstle v. Greenpeace
Greenpeace brought proceedings against Professor Oliver Brüstle to revoke his patent on a method for transforming hES cells (derived from an existing cell line) into nerve cells. They argued that hES cells are excluded from patentability by the morality clause in the "Biotech Directive". In 2011, the German court referred the case to the ECJ, asking for clarification of the "Biotech Directive" on three points:
- What is meant by the term "human embryo"?
- What does the exclusion from patentability of "human embryos for industrial or commercial purposes" mean?
- If a patent does not explicitly mention hES but their use is required, should the patent be granted?

The Findings of the ECJ[5]
- A "human embryo" encompasses any fertilised or non-fertilised human egg, and any non-fertilised egg whose further development has been stimulated by genetic modification. Referring courts are to decide whether an hES cell constitutes an embryo.
- The use of embryos for scientific or medical research is not patentable in itself unless it is associated with an invention which can be useful to embryos.
- Inventions which require the prior destruction of human embryos, or their use as base material are not patentable even if the patent does not refer to their use.

Implications of the ECJ Ruling

The full implications of the ECJ ruling are still under examination by the UK Intellectual Property Office. However, it is thought that the ruling prohibits patenting of inventions which directly use hES cells or have used them in their development. It does not prevent the use of hES cells in research and some suggest the judgement provides a freedom to operate without risking patent infringement.

Concerns have been raised over who will fund hES cell research in the future if a patent cannot be obtained. After the ECJ ruling, the UK government announced it will continue to fund such research, but there are concerns that private companies may invest outside of Europe where they can obtain patent protection. However, this is not a straight-forward transfer of investment, as hES cell research is prohibited or restricted in some countries. It may be possible to patent downstream processes instead of the hES cells themselves. For example, Europe's first clinical trial using hES cells (testing a UK-developed treatment for age related sight loss) is unaffected by the ruling as the researchers patented the method of delivering the hES cells to the back of the eye rather than the cells themselves.

Ethical Assessment of Patent Applications

Bodies such as the Nuffield Council on Bioethics have questioned whether patent offices have the institutional competence to execute the morality exclusion.[6] In response to the "Biotech Directive" Norway established a specialist Advisory Board on Ethical Aspects of Patenting. The Board's role is to assist the patent office in assessing applications which present moral difficulties. Since its formation in 2004, only one patent application (concerning a genetically modified salmon) has been referred to the Board. In this case the patent office elected not to follow the Board's recommendations and granted the patent. The Norwegian Ministry of Justice is considering changes to its national patent law to strengthen the Board's position.

Innovation and Patient Access

Research and development in therapeutics and diagnostics is often expensive and time consuming. The granting of a period of market exclusivity (up to 20 years)[8] through patent protection is one way of providing an incentive for innovation. Many diagnostics companies view biomarker patents as necessary, if they are going to develop clinical applications which utilise them. Even in the public sector, researchers funded by charities are encouraged to gain intellectual property on technologies arising from their work, to ensure that the healthcare benefits can be realised.

Patents can both help and hinder knowledge transfer. On the one hand, they ensure public disclosure of information. On the other, broad patents and restrictive licensing may lead to monopolies in service provision. While such monopolies often limit patient access and increase prices, they can also result in increased patient benefit (Box 6).

Licensing and Innovation

A potential barrier to innovation, particularly in the area of gene patents, is that companies wishing to commercialise new technologies may have to acquire multiple licences from different rights holders. However, there are mechanisms which can be used to ease the way.

- **The formation of a patent pool**, which usually requires patents relating to a particular technology to be bundled into a defined licensing package. Patent pools have been used successfully in the electronics sector to generate cost effective licensing agreements, but their use in biomedical technology may present challenges. For example, it may be difficult to identify all the gene patents needed to eliminate the risk of infringement.[7]
- **Compulsory licensing**, a mechanism by which a Government can allow use of a patented invention without the consent of the patent holder. The TRIPS agreement sets out provisions and requirements for compulsory licensing.[8]
- **Patent clearinghouses** are collections of commercially viable yet unused patents. They offer reasonable, non-exclusive licences, circumventing the need for licensing negotiations. Clearinghouses are generally easier to set up and cheaper to run than patent pools and have already been successfully implemented in the biomedical sector. For example, GSK set-up a clearing house to enable researchers to develop therapeutics which treat neglected tropical diseases in developing counties.[7]

Box 6. Digene Diagnostic Test for Cervical Cancer Screening[9]

Digene (now Qiagen) was a US molecular diagnostics company which held patents for the high-risk viral strains associated with cervical cancer. Its patents gave the company a virtual monopoly in the US market for genetic testing to detect these strains in patient smear samples for over a decade. Digene faced resistance to uptake of their test, both inside and outside the USA as the smear test is an existing and effective method of screening.

Several interested parties have highlighted that it is relatively easy to get a diagnostic test to market.[10] They suggest that the regulations assess only the safety of the tests rather than how well they work and argue that getting a genetic test to market should require more clinical evidence to prove efficacy. In the case of Digene's HPV test, the company invested heavily in providing a clinical evidence base to prove the efficacy and advantages of their test in order to increase uptake outside the USA. But it was able to make this investment only because it had a patent which gave it a monopoly in the US market.

Patient Access

While patents are considered a key driver for biomedical innovation, there are concerns that they can have a negative effect on patient access to medical services, particularly with respect to high quality diagnostic tests. Many of the genetic tests currently offered by the NHS are for rare inherited disorders. Most of these tests have been developed in-house by the NHS and may infringe existing intellectual property rights.[10] However, the number of patients undergoing any single such test is low, so the incentive for enforcing a patent is limited.

Currently patient access to genetic tests in the UK is largely unrestricted by patents. This is because most genetic tests are conducted by the NHS rather than by private companies. Even where these tests infringe patents, rights holders are unlikely to challenge the NHS because this would be expensive and has the potential to generate bad publicity.[11] It is likely that the number of biomarker-based tests offered by the NHS will increase in the coming years. These tests allow the tailoring of medical treatments to patients. There are concerns that as the number of tests increases, this will make it more commercially attractive for companies to pursue patent infringements.[11] Groups such as the UK NHS Genetic Testing Network suggest that it is not clear where NHS laboratories can get an overview of the patent landscape or who is responsible within the NHS for addressing intellectual property issues.

Endnotes

1 BIS: Economics paper No. 2 Life Sciences in the UK (January 2010)
2 Biotechnology Directive 98/44/EC
3 Parthasarathy, *Community Genet,* 2005, 235
4 www.genomicslawreport.com
5 European Court of Justice Judgement Case -34/10-Brüstle
6 Nuffield Council on Bioethics (2002) The ethics of patenting DNA
7 OECD (2011), Collaborative Mechanisms for Intellectual Property Management in the Life Sciences
8 Agreement on Trade-Related Aspects of Intellectual Property Rights
9 Hogarth, S., Hopkins, M., Rodriguez, V., *Sociology of Health and Illness*, 2011.
10 Human Genetics Commission (2010), Intellectual Property & DNA Diagnostics
11 Hawkins, N. *Genetics in Medicine,* 2011, 1.

POST is an office of both Houses of Parliament, charged with providing independent and balanced analysis of policy issues that have a basis in science and technology. POST is grateful to Kate Hamer for researching this briefing, to the BBSRC for funding her parliamentary fellowship, and to all contributors and reviewers. For further information on this subject, please contact the co-author, Peter Border.