Europe says 'hello Dolly' to the biotech directive

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Nearly a decade after it was first proposed, the European Biotechnology Directive has finally been passed into law. The main purpose of the Directive is to provide a uniform set of legal rules that will apply to biotechnology patents throughout the 15 countries of the European Union. The authors describe how the Directive confirms that, subject to meeting the normal criteria, patents can be granted for inventions involving DNA, cell lines, microorganisms, plants, animals and human-derived material. However, on moral grounds, patents will not be allowed for certain inventions involving human cloning, germ-line gene therapy, human embryos or transgenic animals.

On 30 July 1998, the European Biotechnology Directive (officially known as the European Parliament and Council Directive on the legal protection of biotechnological inventions[1]) came into force. In essence, the Directive requires that all member states in the European Union apply the same criteria in deciding whether to grant patents for biotechnological inventions, including genes, cell lines, microorganisms, plants and animals. The Directive was the subject of a vigorous debate that lasted nearly a decade, and the final version represents a compromise between those who regard the availability of patent protection as essential for the development of a strong European biotechnology industry and those who think that allowing such patent protection raises serious ethical and other concerns.

Background

The potential economic importance of modern biotechnology in medicine, industry and agriculture began to be widely recognized in the early 1980s. As far back as 1983, the European Commission noted that there was a European lack of strength in the field compared with the USA and Japan and so began funding initiatives to remedy the situation. One of the factors that the European Commission identified as contributing to Europe's underperformance was the uncertainty surrounding the availability of patent protection for biotechnological inventions in the various countries of the EU (or the European Community, as it was then). No one knew, for certain, which European countries would allow biotechnological inventions to be patented or, in countries that would allow such patents, whether all biotechnological inventions, including human genes and living organisms such as bacteria, plants and animals, could be patented in those countries.

By contrast, the situation in the USA was becoming much clearer. A Supreme Court decision in 1980 (Ref. 2) had shown that genetically engineered microorganisms could be patented in the USA. This paved the way for the US Board of Patent Appeals in 1985 to decide that transgenic plants could be patented, and an announcement in 1987 by the US Patent and Trademark Office that, in principle, it considered all non-naturally occurring non-human lifeforms, including animals, to be patentable.

The first proposed Directive

Against that background, the European Commission announced in 1985 that it intended to introduce measures concerning patent protection of biotechnological inventions. It published its first proposal in 1988. The proposed Directive was essentially legal and technical in character, and basically, was intended to lay down a fairly short set of legal rules on the patent protection of biotechnological

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inventions that would be followed by every member state of the EU. The draft actually did very little to address any of the public's ethical or safety concerns relating to genetic engineering. These issues were under consideration by the European Commission and the various national governments. However, it was generally thought that they would be adequately dealt with both by an existing prohibition in patent law that prevents inventions that are contrary to public order or morality from being patented, and by measures such as enforcement of proper standards of animal welfare and regulation of research on recombinant lifeforms and their release into the environment.

It soon became clear, however, that the draft Directive would have to be modified before it would be acceptable to the European Parliament. The very idea of allowing patents for some, or even all, biotechnological inventions was considered unacceptable by various groups. Most people would accept that human beings, in themselves, should not be patentable, but there were differing opinions on the desirability of allowing human DNA or cell lines to be patented. Furthermore, not everyone agreed that patents should be granted for living matter such as plants and animals, especially transgenic animals which might suffer as a result of being genetically engineered. Many academic scientists, in particular, were worried that they could be prevented from doing research on patented genes, and also argued that genes found from nature were simply discoveries and could not be the subject of a patentable invention.

Around the same time as the Directive was being introduced and considered by the European Parliament, several well-publicized events also occurred that heightened the public's concerns about biotechnology. In Europe, the European Patent Office (EPO) granted a patent for the 'Oncomouse' (although the patent is still the subject of a legal challenge). In the USA, the National Institutes of Health filed applications for patent protection on expressed sequence tags (ESTs). These applications were subsequently withdrawn, but there are still outstanding applications for patents on ESTs by other organizations. There was also continuing publicity concerning the case of John Moore, who objected to the patenting by the University of California and his physician of a cell line which had been developed from a cell taken from his spleen. In addition, there were controversies surrounding the filing of patents by organizations in the developed countries for inventions involving the use of genetic materials taken from developing countries.

Despite various efforts to amend the proposed Directive, it continued to be unacceptable to many Members of the European Parliament, and a conciliation committee was formed in late 1994 to produce a text that was mutually acceptable. However, the revised text was ambiguous and unclear and many in the biotechnology industry were now questioning whether there was any need for the Directive. Much of the debate over the Directive had been hostile to the industry and, by 1995, developments in patent law had resolved some of the uncertainties that existed in 1988. In any event, the amended Directive failed to gather sufficient support in the European Parliament to be passed into law and it was finally rejected in March 1995.

The second proposed Directive

Notwithstanding the problems encountered by the first proposed Directive, the European Commission was still concerned about the gap between the European and US biotechnology sectors. It pointed out that four out of the five world's most successful biotechnology companies were based in the USA and that a disproportionate number of biotechnology patents originated in the USA. It argued that differences and uncertainties in patent law still existed among member states and that the need for unifying legislation had not diminished. In December 1995, the European Commission therefore proposed a new Directive, based heavily on the final text of the version rejected by the European Parliament, but with clarifications in several areas.

The European Parliament proposed 66 amendments to this new proposed Directive, of which 65 were accepted by the European Council of Ministers and incorporated into another revised text. Opponents of the measure failed to gather enough votes in the European Parliament to force any further amendments and the Directive was formally approved on 12 May 1998. It came into force on 30 July 1998 and EU member states now have two years to implement the Directive by giving its provisions the full force of national law.

Preamble to the Directive

The Directive contains 56 introductory paragraphs, known as recitals, and 16 operative provisions, known as articles. The recitals basically set out some of the background behind the Directive and can be used to provide some guidance as to its intended effect. They can become very important where there are inconsistencies, gaps or ambiguities in the articles of the Directive. In addition, although many of the recitals deal with specific types of biotechnological inventions, such as genes and genetically engineered plants and animals, or address specific ethical concerns, they do contain some important general statements.

The recitals start with the recognition that biotechnology and genetic engineering are playing an increasingly important role in a broad range of industries and that adequate legal protection is required to make R&D in the field profitable. They state that the legal differences for protection of biotechnological inventions that exist within the EU may act as a disincentive to trade or affect industrial development; thus effective legal protection, available on the same basis in all the EU member states, is essential to maintain and encourage investment in biotechnology. That said, however, the recitals acknowledge that human dignity and integrity and other ethical and moral principles should be respected by patent law.

One of the recitals also makes clear that the grant of a patent simply allows its owner to prevent others from exploiting the patented invention. In other words, the patent owner must still comply with laws and regulations in areas such as public health, safety, environmental protection, animal welfare, the preservation of genetic diversity and compliance with ethical standards. Although this merely confirms an existing principle of patent law, this concept was one of the most difficult for supporters of the Directive to explain to opponents within the European Parliament, to whom owning a patent concerning a DNA sequence for a gene was synonymous with actually 'owning' the gene.

The main provisions of the Directive

Patentability of biological materials

It should first of all be remembered that the Directive does not alter the basic principles of patent law, which are that for an invention to be patentable it must be:

- New
- Not obvious to a person of ordinary skill experienced in the relevant technology
- Have an industrial application

As a further condition for any patent to be valid, the applicant should provide a clear and complete enough description in the patent to enable someone of ordinary skill in the field to reproduce the invention without undue experimentation or further invention. This condition is imposed because the *quid pro quo* for granting a patent (which confers the potentially valuable right to stop others from using the invention for the lifetime of the patent) is considered to be the contribution to knowledge that is made by publication of the information contained in the patent.

The first operative provision in the Directive states that EU member states should protect biotechnological inventions under their national patent in accordance with the Directive. This is clarified by a subsequent provision, which specifically states that inventions concerning 'biological material' will be patentable provided that they meet the normal requirements of patentability. Since 'biological material' is defined as 'any material containing genetic information and capable of reproducing itself or capable of being reproduced in a biological system', it must include living organisms, genes, DNA and RNA. Thus, in principle, the Directive ensures that most types of biotechnological inventions should be patentable throughout the EU.

In addition, the Directive confirms that biological material that previously existed in nature, but is isolated from its natural environment or is produced using a technical process, may be the subject of an invention. This is to address the issue of what is a discovery and what is an invention. For instance, if a gene is found for a previously undescribed plant protein, the gene sequence is elucidated and the protein is expressed in bacteria, it might be possible to patent, for instance, a vector containing the relevant DNA sequence, the purified protein itself and a process for the protein's expression and purification. However, the scope of the patent could not include the gene or protein in the form in which they naturally exist in the plant. Thus, the patent could not be used by its owner to prevent continued cultivation of the plant by farmers or gardeners.

Materials of human origin

The patenting of human DNA and other human-derived material deeply concerned many members of the European Parliament and failure to agree over the issue was a major reason why the first proposal for the Directive was rejected. There is therefore special provision in the Directive to clarify the circumstances in which human-derived material may be patented.

The Directive explicitly states that the human body, at the various stages of its formation and development, and the simple discovery of one of its elements (including a gene sequence), cannot be patented. However, it confirms that, like other biological materials, an element isolated from the human body or otherwise produced by means of a technical process (including the complete or partial sequence of a gene) may constitute a patentable invention, even if the structure of that element is identical to that of a natural element.

In addition, in an effort to address the issue of whether ESTs are patentable, the Directive goes on to say that the industrial application of a sequence or a partial sequence of a gene must be disclosed in the patent application. In other words, patents are not available for gene sequences without an indication of their function.

Thus, the patentability of human proteins, DNA and cell lines is confirmed by the Directive. However, this will only apply to proteins and DNA that have been isolated from their natural state, and it would not be possible to patent the human body. Moreover, so far as gene sequences are concerned, which might include ESTs, some indication of their function must be given in the patent application.

Ethical and moral issues

As mentioned, issues relating to ethics and morality were hotly debated throughout the passage of the Directive. At first, it was thought that existing patent law adequately dealt with the issues, as there was already a prohibition on the patenting of inventions whose publication or exploitation would be contrary to public policy or morality. However, it soon became clear that this prohibition could be interpreted in many different ways and that many members of the European Parliament were concerned that the Directive might enable patents to be granted for biotechnological inventions that many people in the EU would consider unacceptable.

The Directive therefore makes clear that inventions shall continue to be unpatentable where their commercial exploitation would be contrary to public order or morality. However, as a general guide to interpretation of this rule, the Directive goes on to give an illustrative list of biotechnological inventions which would be excluded from patentability on this ground. These illustrative examples are:

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

In addition to the examples on this list, the Directive also states that inventions for processes whose use would offend against human dignity should also be unpatentable. An example of an invention excluded from patentability on this ground is a process to produce chimeras from germ cells or totipotent cells of humans and animals (such a patent has recently been filed in the USA, reportedly for the purpose of generating a detailed debate there on the extent to which human life is patentable[3]).

Another ethical area that was raised during the debate concerned the commercial exploitation of material of human origin and of the genetic resources of developing countries. The recitals therefore state that information relating to the geographical origin of animal or plant material upon which an invention is based should, 'where appropriate', and if known, be given in the patent application. In the case of material of human origin, the recitals also state that the person from whose body it is taken should be given the opportunity to give free and informed consent to the application for a patent. It is unclear whether failure to comply with these requirements would necessarily result in the rejection of a patent application. It is also unclear how this would apply to material derived from existing tissue and other samples where such consent has not been obtained and the donor is untraceable.

Finally, the Directive places a responsibility on the European Commission to provide the European Parliament periodically with various reports on the impact of the Directive and developments in patent law. These reports cover areas such as the relationship between the Directive and international agreements on the protection of human rights; whether the Directive affects the publication of scientific papers and whether this has any implications on basic genetic engineering research; and the development and implications of patent law in the field of biotechnology and genetic engineering.

Animal and plant varieties and 'farmer's privilege'

Plant and animal varieties, at least as produced by conventional breeding methods, have always been considered unpatentable in many European countries. Indeed, a separate intellectual property right, known as a plant variety right, is available in the EU for new plant varieties. Difficulties have been experienced, however, in deciding whether plants and animals produced by genetic engineering should be treated for patent law purposes in the same way as varieties produced by conventional methods. The difficulty arises partly because most plant and animal inventions are not confined to any one particular variety. For instance, if a transgenic plant is the subject of the patent, the invention will probably be applicable to any plant within a species and/or a class of related species.

The Directive has attempted to deal with this question by confirming that plant and animal varieties and processes for the production of plants and animals that consist entirely of natural phenomena such as crossing or selection are unpatentable. However, by way of exception to this rule, inventions that concern plants or animals may be patentable if the technical feasibility of the invention is not confined to a particular plant or animal variety. Taken together, this would appear to exclude conventionally bred

varieties of plants and animals and conventional breeding techniques from patentability, but allow plant and animal inventions to be patented that can be applied to whole species or classes of species, rather than single varieties. However, this remains to be tested and, in a case involving Novartis (Ref. 4) under appeal at the EPO, this interpretation has been thrown into doubt.

Further provisions in the Directive also deal with the issue of 'farmer's privilege'. This is probably more relevant for the agricultural rather than the pharmaceutical sector, but is connected with the rights of farmers to save the seeds of a patented plant from one harvest to use for the next year or to use breeding stock or animal reproductive material for the purposes of pursuing their agricultural activity. Essentially, the Directive explicitly allows farmers to use, on their own farms, seeds and other propagating material saved from previous harvests of patented crops. However, the extent to which farmers can use breeding stock and animal reproductive materials will be governed by national law.

Conclusion

The Directive has been welcomed by the pharmaceutical and biotechnology industries. Despite industry reservations over certain provisions of the Directive, overall it confirms that new drugs based on human-derived material such as DNA and proteins, and processes for their production, can be patented throughout the EU. The EPO has a backlog of >2000 applications involving transgenic plants and animals, which it had stopped processing pending passage of the Directive and resolution of the *Novartis* case. It was hoped that the Directive would clarify the position on transgenic plants and animals, but developments in the *Novartis* case may indicate that this hope was unfounded. If so, applicants for patents involving transgenic plants and animals may be forced to go through the more expensive route of separately applying for patents in the national patent offices of the various EU member states rather than making one application for all EU member states before the EPO.

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