

Patenting in Biotechnology

- *New forms of life*
- *The debate about patents in biotechnology*
- *International developments*
- *EC directive on protection of biotechnological inventions*

The techniques of genetic modification allow novel characteristics to be introduced into living organisms, but there is debate over how far resulting modified life forms should be patentable. US law allows patents to be considered for all modified organisms whether they be micro-organisms, plants or (non-human) animals. In Europe, a European Commission proposal for a Directive is under consideration to endorse the availability of such rights in all European Union (EU) countries.

This briefing paper is an update of the briefing paper "Patenting Life" which was published in June 1993. It considers the scientific developments which have led to the possibility of patenting living organisms or their products, and the concerns about it. The patent law, commercial and ethical considerations pertaining to genetic modification of naturally occurring substances, micro-organisms, plants and animals differ considerably and therefore each category is considered independently. The overall aim of this briefing paper is to provide balanced information and to advance the public debate about these topics.

The paper results from the combined contributions of patent experts, scientists, industrialists and environmental and consumer group representatives from throughout Europe.

NEW FORMS OF LIFE

Recombinant DNA technology is the term used for a series of techniques that can be used to modify the basic genetic make-up of a living organism by inserting (or removing) sections of DNA, a molecule that carries hereditary information. Following the first demonstration of these techniques in 1973, their potential to introduce novel characteristics into microbes, plants and animals has been

rapidly explored. Initial efforts focused on microorganisms because of the relative simplicity of their structure, and a number of commercial processes now use microorganisms which have been genetically "programmed" to produce materials which they would not produce naturally (eg drugs such as human insulin, growth hormone and certain enzymes).

With plants, the intentions of the traditional breeder and the genetic engineer are the same - to insert into or modify the genome to introduce a novel trait. The extra power of genetic engineering comes from its ability to control more precisely the introduction of new traits and to introduce genetic material from unrelated species of plants and from organisms other than plants. Genetically modified plants include varieties with traits such as resistance to herbicides, pests or diseases, enhanced nutritive content and new shade of flower colouring.

Genetic modification of farm animals and fish is still largely at the experimental stage. The aims of research include infection resistance and increasing growth rate. A method for producing pharmaceutical products via farm animals' milk is at an advanced stage of development. The first patented genetically modified animal, which is available for medical research, is a mouse which is genetically predisposed to cancer - for use in testing new drugs or chemicals for carcinogenicity.

The use of recombinant DNA methods in relation to human diseases caused by gene defects (eg cystic fibrosis) is at present concentrated on diagnostic applications but therapeutic applications are also under investigation. The first attempt to modify human body cells in a patient, using the gene transfer technique (somatic gene therapy) was made in the US in 1984. Bone marrow cells which were unable to produce an enzyme essential to the immune system

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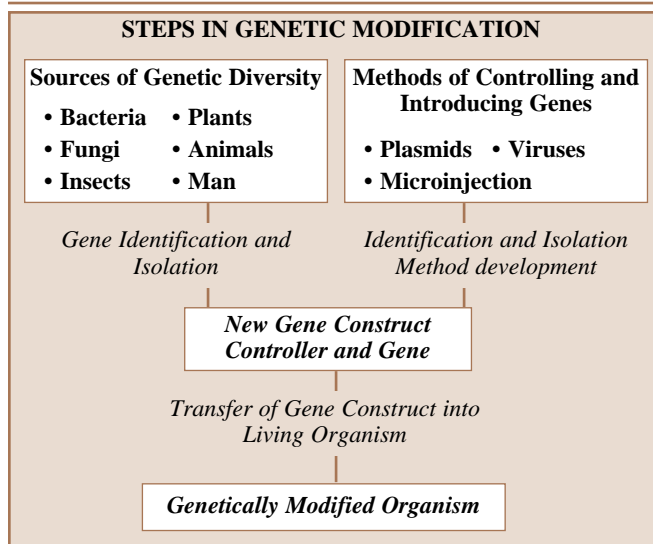
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1

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were removed from the patient, modified to include the gene for the missing enzyme and replaced. This attempt failed, but in 1990 a similar method was successfully used to modify white blood cells genetically. Since then more than one hundred clinical protocols involving gene therapy have been recommended and clinical trials are under way in many countries. More radical and controversial is the proposal for germ line gene therapy. Such manipulation would change the genetic make-up of the eggs or sperm produced by an individual and would be carried on to future generations. The general opinion in Europe about germ line gene therapy is at present strongly negative.

Innovations such as these are clearly industrially significant and potentially valuable to society. Biotechnology companies consider legal protection for these innovations to be essential, as evidenced by the multi-million dollar settlements negotiated in successful patent infringement suits. They therefore insist that there should be no discrimination against legal protection in this field as compared with what is available in other technologies. Patent protection gives the opportunity to the innovator to earn a commercial return on the heavy investment in this research and therefore to fuel the ongoing research necessary for further improvement in *eg* health care and human and animal nutrition.

PATENTS

Patent laws, like trade mark and copyright laws, are an important area of intellectual property protection legislation. In the case of patent laws, they provide protection of inventions demonstrating the key characteristics of novelty, non-obviousness, utility and sufficient disclosure. The grant of a patent confers a civil right on the patent owner to prevent others from exploiting what is claimed in the patent, excluding use for scientific research purposes. It does not permit the patent owner to exploit his own invention (*eg* a patent owner must comply with

national regulations regarding the use of the invention), nor does it confer any right of ownership of patented materials. Patenting in the EU can take place either through national patent offices or through the European Patent Office (EPO) in Munich which affords protection in all, or any selection of, states party to the European Patent Convention (EPC)¹. Practice in the US and Japan is also of considerable relevance to EU inventors and companies, since the US

often provides the largest single market for products developed in the EU; equally the patent protection available to a US or Japanese company in its home market affects its ability to compete in other markets.

Attempts to harmonise patent law and practice internationally have not yet fully succeeded. For example, at present the US allows a one-year grace period between an inventor's publication and the deadline for filing a US patent application. In contrast, any public disclosure of an invention before filing any application is usually fatal to the prospects of protection in European countries. Again, the US settles disputes over priority as between rival claimants for the same invention by comparing actual dates of invention, whereas, in other countries, whoever has the earlier effective patent application date will usually prevail. Therefore patents encourage secrecy up to the point of filing but ensure publication of the information after the granting of a patent, and thus making it available for research purposes.

Another difference is that in US patent law the term "invention" means invention or discovery. In European law "discovery" is distinguished from "invention" and is unpatentable. The distinction is not easy to define. A discovery involves new knowledge whereas an invention is a practical application of knowledge. For example: the elucidation by Crick and Watson of the double helix structure of DNA was an unpatentable discovery whereas later exploitation of this to produce DNA artificially and to produce new forms of DNA have given rise to many patents.

Naturally occurring substances, present as components of complex mixtures of natural origin, can in principle be patented where they are isolated from their natural surrounding, identified, and made available for the first time and a process is developed for producing them so that they can be put

to a useful purpose. This applies to inanimate substances as well as to living materials. In appropriate circumstances such substances are not ruled out as mere discoveries but are considered as invention by the EPO and other legal authorities.

Micro-organism patents are now routinely granted by the US, European and Japanese Patent offices. Although a US patent had been granted in 1873 to Pasteur for "*yeast free from germs of disease as an article of manufacture*", the US courts later held that the "*discovery of some of the handiwork of nature*" was unpatentable. In the Chakrabarty case in 1980 the US Supreme Court decided that a micro-organism was not precluded from patentability solely because it was alive. Thus a *Pseudomonas* bacterium manipulated to contain more than one plasmid controlling the break-down of hydrocarbons (therefore more useful in dispersing oil slicks than the natural organism containing only one such plasmid) was "*a new bacterium with markedly different characteristics from any found in nature*" and hence not nature's handiwork but that of the inventor. The "*product of nature*" objection therefore failed and the modified organism was held patentable. This decision was influential in most other industrially developed countries and the issue is now settled in law.

Plant patents are also obtainable in US, Europe and Japan. The US Plant Patent Act of 1930 is restricted to asexually propagated plants and over 6,500 of such plant patents have been granted (mostly for rose and fruit trees). In the Hibberd case (1985), following the principle established in the Chakrabarty case, it was decided that normal US "utility" patents could be granted for other types of plant *eg* genetically modified plants.

In Europe, patent law was originally considered unsuitable for protecting new plant varieties developed by traditional breeding methods. Special national laws of plant breeder's rights, which are also called Plant Variety Rights (PVR), were therefore established in the 1960s in some countries as well as the International Union for the Protection of New Varieties of Plants (UPOV, 1961). To avoid legal confusion, patent law in Europe subsequently excluded plant varieties from patentability *eg* EPC Article 53(b) which excludes patents for "*plant and animal varieties*" as such and "*essentially biological processes for the production*" of plants and animals. The UPOV Convention was revised in 1991 and now does not prevent dual protection by PVR or patents. This revision awaits ratification by Member States and is therefore not yet in force.

Plant breeder's rights have been highly successful in their own sphere. However, legal experts now generally recognise that

¹ All EU countries, Switzerland, Liechtenstein and Monaco can be covered by a single application.

patent law is better suited to the protection of recombinant methods for producing transgenic plants and the resulting products. Patents of this type, claiming methods and products *per se*, have been granted by the EPO.

Animal breeds produced by traditional methods have no legal system for their protection comparable to plant breeder's rights. Based on the micro-organism and plant patent precedents, the US Commissioner of Patents declared in 1987 that US patents would be granted for "*non-naturally occurring non-human multicellular living organisms including animals*". The first transgenic animal patent was issued in 1988 to Harvard University with claims covering the "oncomouse", one in which an oncogene has been introduced to make the animal more susceptible to cancer and therefore more sensitive in testing possible carcinogens. After initial reluctance by the EPO to grant the corresponding European patent (and a successful appeal to the Appeal Board) the European patent was issued. This is now under formal opposition by anti-vivisection and animal rights groups. More than 300 patent applications for transgenic animals have been filed but so far few have been granted (3 in the EPO, 6 in the US Patent Office).

Gene patents are available in all fields of biotechnology. For recombinant DNA inventions, the patent will claim the nucleotide sequence coding for the protein expression product, vectors *eg* plasmids containing this sequence, micro-organisms or higher organisms transformed with the sequence, and in appropriate cases the expression product itself (normally only if the product is new *per se*). Corresponding process technology will also be claimed. The patentability of DNA sequences of unknown function is dubious and controversial. The Human Genome Organisation accepts that patents should be granted for full length genes but is against patenting fragmentary cDNA sequences having no established utility.

THE DEBATE ABOUT PATENTS IN BIOTECHNOLOGY

The industries that utilise biotechnology are convinced that intellectual property protection should be obtainable for the inventions that stem from research and which have commercial potential. Biotechnology research workers in academic institutions increasingly share this view because of their need for research funding which is in part conditional on patentability. A serious challenge to this assumption has come from a number of interest groups concerned variously with matters of ecology, animal welfare and rights, moral issues and the interests of small farmers and the developing countries.

Some of these groups have formally opposed specific European patents and demanded their revocation. For many such groups "patenting life" is considered unethical in principle. The opposition extends also to possible structural change in the agricultural industry which might stem from biotechnology and especially from the acquisition by the larger corporations of legal rights on the advances that are being made.

Legal and moral issues: A legally permissible ground of objection is that genes are naturally occurring entities and that the methods for transferring them to plants or animals are well-known and straightforward. This is a challenge to the inventiveness content of the particular patent at issue; it is an argument that industrial competitors will sometimes use against each other's patents but so far it has not achieved a high success rate. The argument also lies at the heart of the moral objections many with religious beliefs have to patenting genes. They regard claims of invention, instead of discovery, tantamount to claiming to be God.

Some feel that patenting living things change the relationship between humanity and the rest of nature. This is particularly sensitive as regards animals, where patents are seen as conferring "ownership", thereby undermining the animal's right to independence of being and relegating it to the status of a mere object. However, plants and animals are owned by the farmers who produce them and use them as agricultural commodities. All such owners, whether of patented or unpatented organisms, are bound to respect animal welfare legislation.

The opposers can raise the morality issue where the patent law allows, as in Europe under EPC Article 53(a) which forbids patents for inventions "*the publication or exploitation of which is contrary to 'ordre public' (public order) or to morality*". The morality objection is being currently used against the European oncomouse patent. To programme an animal genetically for certain death in laboratory experiments is morally repugnant to these opposing groups and they feel in conscience bound to protest. Animals have, however, long been used as disease models. The response of the patent authorities may depend on whether, in the light of general public acceptance of the use of test animals in research to find cures for serious human diseases, the use of the oncomouse would be generally condemned.

The objection to animal suffering may also apply to the genetic modification of farm animals. One early experiment to insert a

EXAMPLES OF US & EPC PATENTS ON ORGANISMS AND GENES	
	<i>Patent number</i>
Isolated gene coding for enzyme involved in penicillin biosynthesis.	US 4,885,251
Isolated gene coding for human erythropoietin, a hormone stimulating growth of red blood cells.	US 4,703,008 EP 148,605
Recombinant plasmids and transformed micro-organisms expressing precursor of the enzyme chymosin (rennin).	EP 077,109
Pseudomonas with multiple plasmids for degrading hydrocarbons (Chakrabarty, see text)	US 4,259,444
Insecticidal Bacillus thuringiensis strain	EP 178,151
Pesticidal (trypsin inhibitor) gene transfer from cowpea to cereals	US 5,306,863
Plant gene/promoter	EP 122,791
Maize seed and plant enriched in tryptophan (Hibberd)	US 4,581,847
Oncomouse (Harvard, see text)	US 4,736,866 EP 169,672
Immunodeficient mouse for study of auto-immune disease	US 5,175,384
Expressing pharmaceuticals in milk of farm animals	US 5,322,775
Herbicide resistance plants	EP 242,236

growth hormone gene into a pig in order to increase growth rate succeeded but caused severe unforeseen side effects including arthritis. Animal welfare groups argue that patents will encourage more research on animal genetic modification, which they oppose on grounds of possible suffering and of principle. Intended to prevent undue suffering, legislation requires the granting of animal experimentation licenses and full disclosure of the experimentation.

Freedoms for breeders and farmers are seen by some groups as threatened by patents on transgenic plants and animals. Under PVR breeders previously enjoyed the so-called "breeder's privilege" or "research exemption" which gave them the freedom not only to use protected plant varieties in their breeding programmes but also to commercialise the further varieties developed therefrom (often only "cosmetically" different from the original) without any royalty payment to the owner of the initial variety. The UPOV Convention as revised in 1991 now expands the scope of the right of the initial variety breeder to include what are termed "essentially derived varieties" (both the terms "essentially derived" and "variety" are defined). This expansion of the right is not automatic but depends on Member States amending their national PVR legislation in conformity with UPOV 1991.

Freedom to research and to commercialise: The freedom to research is safeguarded equally under both patent law and PVR law. But the freedom to commercialise the resulting products of research depends on whether or not they infringe the patent claims or are "essentially derived" under PVR law. A strengthened UPOV-type protection would therefore go part of the way towards the strong protection given by patents. Neither system is a threat to the free use of existing germ plasm since these rights can in no

sense monopolise known material as such. Again, until the UPOV revision is taken up in national laws, farmers legitimately sowing seed of a protected variety are legally free to save part of the seed from the first crop of plants for sowing on their own farms to produce a second and subsequent crops (the “farmer’s privilege”). Recognising that the current scale of use of farm-saved seed thus deprives the breeder of significant royalty income, the strengthened right under the 1991 version of UPOV would make this subject to authorisation of the breeder. However, Contracting States can “re-introduce” this freedom under their national legislation “within reasonable limits and subject to the safeguarding of the legitimate interests of the breeder”.

INTERNATIONAL DEVELOPMENTS

(1) The United Nations Convention on Biological Diversity, enacted in June 1992 and entering into force in December 1993, has been ratified by 157 States to August 1996. It aims to ensure conservation of biological diversity, sustainable use of genetic resources, and the fair and equitable sharing of the benefits from their utilisation.

Genetic resources have in the past been declared “a common heritage of mankind to be preserved, and to be freely available to all, for use for the benefit of present and future generations”. However, in this Convention, Article 15 now recognises the sovereign rights of States over their natural resources, their authority to determine access thereto, and the need for access to be subject to prior informed consent and on mutually agreed terms. In return for providing access to its genetic resources, a donor country should benefit through any of three mechanisms:

- participation in research, Article 15(6),
- sharing in the results of research and proceeds of commercial exploitation, Article 15(7), and
- access to and transfer of derived technology, Article 16(1).

The Convention recognises a legitimate role for intellectual property in achieving these objectives.

(2) The Uruguay round of the General Agreement on Tariffs and Trade (GATT) created a subsidiary Agreement on Trade Related Aspects of Intellectual Property Issues (TRIPS). Any country ratifying GATT accepts the obligation to establish minimum standards of intellectual property. Patents are to be available in all fields of technology except where exploitation of the invention must be prevented to protect ‘ordre public’, human,

animal or plant life or health or to avoid serious prejudice to the environment.

TRIPS allow Members to provide exclusions from patentability similar to those found in the EPC (see above) but they must provide for “the protection of plant varieties either by patents or by an effective sui generis system or by any combination thereof”. (A sui generis system is one devised for its own special purpose.)

EC DIRECTIVE ON PROTECTION OF BIOTECHNOLOGICAL INVENTIONS

The proposed draft of an EU Directive on the Legal Protection of Biotechnological Inventions was originally published in 1988. After several years of debate, a version of this proposal was agreed by a joint committee of the European Parliament (EP), the European Council and the European Commission but was voted down in plenary session of the European Parliament in March 1995. The European Commission published a revised proposal in December 1995. The Directive aims at harmony in the EU between national patent laws and the EPC, and a uniform legal interpretation on some points of special relevance to living systems.

The Directive is addressed to patent issues relating to “biological material”, which is defined in Article 2 as any material containing genetic information and capable of self-reproducing or of being reproduced in a biological system. This must therefore cover living matter, viruses, genes and other types of DNA and RNA. Although Article 3 excludes patents on the human body and its elements in their natural state, elements isolated from the body or otherwise produced by a technical process can be patented if they are capable of industrial application. Article 4 provides that no invention is to be refused patent protection for the sole reason that biological material is involved. This principle has been confirmed for many years in patenting jurisprudence in the major industrial countries. Article 4 provides specifically for the patentability of plants and animals and parts of these except for “Plant and animal varieties”.

Natural products which have biological utility can qualify for patent protection in certain circumstances (usually as the purified material). Article 8 of the Directive confirms that patents for these products should not be ruled out in principle as mere “discoveries”. Thus the presence of a product as part of a pre-existing material is not alone a sufficient ground for refusing a patent for it.

By Article 9, inventions are not patentable where their exploitation would be contrary to ‘ordre public’ or morality. The EPC and laws of most Member States already

contain a similar exclusion *eg* in EPC Article 53(a) mentioned above. However, Article 9 goes on to specify particular examples which for this reason cannot be patented. Paraphrasing the actual text, these include (a) methods of human germline gene therapy² and (b) any genetic modification of animals which causes suffering disproportionate to the likely benefit to man or animal.

Article 10 confirms that a patent on a biological material (or a process for producing it) covers the first and all subsequent generations of material obtained by multiplication or propagation provided the crucial characteristics of the original are retained. Patent rights in a product normally become exhausted when the product is marketed by the patent owner or a licensee. However, for a product which can be multiplied biologically, the purchaser can obviously propagate the purchased product for the purpose implied in the sale, but Article 12 forbids the resulting material being used in further cycles of multiplication or propagation. Article 13 provides an important exception to this rule, allowing farmers to re-sow seed saved from the first crop. This “farmer’s privilege” in patent law is to be limited, however, in order to be in line with the corresponding provision in the EU regulation on an EU plant breeder’s right. The new EU plant breeder’s right provides for a royalty payment on farm-saved seed which is “sensibly lower” than that for bought-in certified seed. Animal farmers are also free to breed from the patented animal for renewal of their own stock.

Article 14 covers the situation in which a third party has bred a new plant variety from a patented transgenic plant and has obtained a plant breeder’s right for it. If, to exploit the variety, the breeder needs a licence from the patent holder but has been refused one, a compulsory licence must be granted, “subject to payment of an appropriate royalty”. This is dependent on the proviso that the new variety constitutes “significant technical progress” and the licence is “dictated by the public interest”. Article 14 is objected to by the agrobiotechnology industry because it detracts from the patent right in an unprecedented way.

General reactions to the revised proposal have been mixed. For example, the Legal Affairs Committee of the EP has raised a number of questions, the European Alliance of Genetic Support Groups are in favour while Greenpeace has expressed a negative opinion. The first plenary EP vote will probably be in 1997. The European Commission’s proposal envisages Member States implementing the Directive by 1 January 2000 at the latest.

² Such methods are already excluded in EPC and European national laws.