Protecting biotech inventions in Europe

The question of what constitutes patentable subject matter is particularly relevant to biotech inventions, not least due to the ethical issues they present. Answers can be found in the EPC 2000 and in EPO case law and practice

By **Julia Molitor** and **Regula Rüedi**,
E Blum & Co AG

Biotechnology is a fast-moving field of science. Although of undisputable benefit, biotechnological inventions often pose ethical challenges. The patenting of the human body, human cloning, transgenic animals and plants raise socio-political issues which have been addressed by the legislature, and case law continues to evolve on the patentability of biotechnological inventions.

A question of interest for researchers in this field is thus what is patentable under the European Patent Convention (EPC). This article reviews patentable subject matter in Europe and addresses how claims should be drafted.

Legal framework

Biotechnological inventions must meet the same patentability criteria as inventions in different technological fields. Briefly put, they need to be new, involve an inventive step and be susceptible to industrial application.

The Administrative Council of the European Patent Organisation incorporated EU Directive 98/44/EC on the legal protection of biotechnological inventions, also known as the Biotech Directive, into the Implementing Regulations of the EPC in September 1999. The revised European Patent Convention (EPC 2000) which came into force in December 2007 includes further provisions and specified terms. It still refers to the Directive 98/44/EC as a supplementary means for interpretation of the legal provisions laid down in the EPC. This article deals only with the regional European patent system and not with the national laws, which may still differ to some extent (eg, see the Swiss Patents Act).

Nucleotide and amino acid sequences

It has long been established that isolated DNA fragments do not represent a discovery and are eligible for patenting, but the ethical and legal controversy nonetheless continues. According to European Patent Office (EPO) case law and practice, DNA sequences are considered chemical compounds, and as such a patent granted for a DNA sequence will confer protection to the holder on all uses of the DNA.

Opponents argue that this absolute compound protection is too far reaching and should be limited – at least for DNA sequences that are identical to naturally occurring sequence – to a specific use of a sequence (eg, "Gene X for the diagnosis of breast cancer"). They fear patent stacking, which could discourage further product development or increase the costs of pharmaceuticals or diagnostic methods, as high royalty costs might be involved.

In spite of these criticisms, it is still sufficient, according to the EPC, that a claim on a nucleic acid or a protein defines the compound by its technical features.

A typical claim drawn to a nucleic acid sequence – be it DNA or RNA – or to an amino acid sequence may be generalised by reference to homology percentages. In the

case of DNA sequences, 50% homology was allowed, while a homology limit of at least 40% was deemed to be too low to ensure that the "same" protein was encoded by the degenerated DNA sequence. If nucleic acid or amino acid sequences are disclosed in an application, the description must contain a sequence listing and information on the function of the sequence.

A claim directed to a structural gene characterised only by its function (eg, "A DNA isolate consisting essentially of a DNA sequence encoding protein X") may be allowable only if protein X is clearly defined in the description and is sufficiently characterised by structural features. In contrast, a protein defined only by its function would not be allowable subject matter, as it might have more than the disclosed functions and thus the requirement of clarity would not be met. Nevertheless, monoclonal antibodies may be claimed as: "A monoclonal antibody X which binds to antigen B." However, if antigen B is closely similar to the known antigen A for which monoclonal antibodies are known, novelty will be recognised only if monoclonal antibody X is defined by technical features distinguishing it unambiguously from the monoclonal antibodies of the prior art.

A further commonly used possibility to characterise a DNA sequence involves stating that it hybridises to a specific DNA sequence. Such claims are allowable only if the hybridisation conditions are defined in the claim.

Single nucleotide polymorphisms (SNPs) are important tools for biomedical research and diagnosis – for example, for elucidating the development of diseases or the body's response to pathogens and drugs, and therewith the development of personalised medicine. SNPs are frequently found all over the genome; therefore, the skilled person would expect to find SNPs in any portion of a genome of a given length, which is why inventive step may become an issue for patenting SNPs. Patentability will be acknowledged if the SNPs are linked to a specific phenotypic trait and thus qualify as "characterised SNPs". In contrast, the EPO regards uncharacterised SNPs – that is, those which are not linked to any specific trait – as lacking inventive step, because the gene to which they belong is known and/or their identification involves routine technology. However, inventive step may be acknowledged if the parent sequence on which the particular SNP resides is novel and inventive. As characterised SNPs are typically linked to a specific use, they are deemed to be susceptible of industrial application.

Haplotypes are combinations of SNPs, typically in a particular gene. The EPO acknowledges that the assessment of inventive step of a claim drawn to a haplotype is a challenge for the EPO.

For a nucleic acid sequence, the industrial application must be indicated in the description. Stating that the sequence fulfils a generally useful function (eg, use as a probe) will not give rise to a distinguishing effect, as this applies to all nucleic acids. Consequently, inventive step and/or industrial applicability could not be acknowledged.

Further to its amino acid sequence, a protein may be claimed by characterising its biological activity in a given assay X, its molecular weight and its pI. Furthermore, a protein may also be defined by its tertiary structure (ie, by structural coordinates). However, if the prior art teaches a protein from the same source organism having the same specific function and approximately the same molecular weight, identity of the two proteins may be expected and therefore problems consist in establishing novelty

Crystals of known proteins are patentable, too. Crystals can be, for example, suitable to provide the protein in a stable form and in high purity or for the determination of the three-dimensional structure, and are therefore industrially applicable. Further to the characterisation of the crystal structure, its method of production needs to be described.

Transgenic plants

Although individual plant varieties are non-statutory subject matter in accordance with the EPC, broad claims directed to transgenic plants which are not drawn to individual plant varieties are obtainable. Due to their lack of stability in some trait over the whole generation population, hybrid seed and plants from such seed are not considered as plant varieties and are thus patentable. Plant cells are to be treated as micro-organisms and are consequently patentable subject matter.

Transgenic animals

Transgenic animals are often used as animal models and provide a benefit in particular in biomedical research – for example, for the understanding of the role of genes in specific diseases or for the development of new treatments and cures for diseases. In contrast to individual plant varieties, which may obtain protection under the UPOV system, there is no *sui generis* protection

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system for animal varieties. In parallel to plants, broad claims drawn to transgenic animals encompassing a number of individual animal varieties are allowable. However, animal welfare is a moral concern which has been addressed by the EPO and was incorporated into the EPC 2000: if the modification of the genetic identity of the animals would be likely to cause them suffering without any substantial medical benefit to man or animal, patentability will be denied.

Stem cells

Isolated elements of the human body are patentable as long as they do not constitute a mere discovery. Consequently, foetal and adult stem cells, such as haematopoietic stem cells, mesenchymal stem cells and olfactory bulb stem cells, are patentable subject matter. However, the patentability of human embryonic stem cells (ie, stem cells derived from early-stage embryos) is a hotly debated issue.

As recently confirmed by a decision of the Enlarged Board of Appeal (G02/06), the use of human embryos for industrial or commercial purposes is not patentable under the EPC. In 1995 the Wisconsin Alumni Research Foundation filed a patent application on a method for obtaining embryonic stem-cell cultures from primates, including humans. The claimed cell culture involved the destruction of human embryos, although this method step did not form part of the claim. Patent grant was denied and the applicant appealed. The case was finally referred to the Enlarged Board of Appeal, which decided that under the EPC it is not possible to grant a patent for an invention which necessarily involves the use and destruction of human embryos. The Enlarged Board of Appeal deemed it irrelevant that after the filing date the same product could be obtained without having to recur to a method necessarily involving the destruction of human embryos, as the use of embryos is within the prohibition of the legal provisions.

However, the Enlarged Board of Appeal stressed that the decision did not concern the general question of human stem-cell patentability.

Deposit

Importantly, if the subject matter of the invention involves the use of biological material (ie, a specific micro-organism or a cell line) which is not publicly available and cannot be sufficiently described, a deposit must be made by the filing date or the priority date of the application at a depositary institution recognised by the Budapest Treaty in order to provide an enabling disclosure. Plasmids, cell lines and micro-organisms of general availability need not be deposited. From the date of publication of the application, any interested person can request a sample of the material. Alternatively, the applicant can choose the so-called “expert solution”, whereby the availability is effected only by the issue of a sample to an expert nominated by the requester. Non-compliance leads to a lack of enablement rejections and subsequent refusal of the application.

Essentially biological and microbiological processes

Essentially biological processes for the production of plants or animals are not patentable. This does not apply to microbiological processes and products thereof which are deemed to be patentable.

Processes are essentially biological if they consist entirely of natural phenomena such as crossing or selection. Patentability of essentially biological processes is denied due to the lack of a technical step.

According to case law, whether a process is to be considered as “essentially biological” must be judged on the basis of the essence of human intervention, taking into account the totality of human intervention and its impact on the result achieved. But the need for human intervention alone is not sufficient for something to qualify as not “purely biological”. Without contributing anything beyond the trivial level, human intervention will not be sufficient to take a claimed process outside the patentability exclusion; thus, the crucial issue is to determine what kind of human intervention is required.

Would the use of molecular markers for selection purposes be sufficient to fall out of the patentability exclusion? At the end of 2008, two referrals to the Enlarged Board of Appeal were pending in relation to the construction of the term “essential biological processes”.

Research tools and reach through claims

During the rapid development of the biotech industry in the 1990s, large numbers of screening tests, assays and research tools were developed. Many applicants were interested in extending protection to the candidate compounds that can potentially be identified by a claimed screening method. A similar situation occurs when the applicant claims a protein which is sufficiently described and also

wishes to obtain protection for possible inhibitors or agonists for the protein.

Claims drawn to these compounds yet to be identified are the so-called "reach-through" claims and are not allowed by the EPO. The reasoning behind this is that reach-through claims go beyond what was actually discovered, as the candidate compound is defined not by technical parameters, but only by reference to the screening method used to identify the compound or – in case of the protein example – the result to be achieved.

The EPO will issue a rejection for lack of clarity, support and sufficient disclosure.

Special cases are *in silico* screening methods, which are often used in drug design. The EPC excludes the patenting of mathematical methods and presentations of information as such; however, *in silico* screening methods are considered to be patentable inventions, as these methods give a technical contribution by use of technical data. The application should include working examples for reasons of sufficient disclosure.

Conclusion

The requirements for patenting biotechnological inventions are manifold and need to be addressed when drafting the patent application. Since biotechnology is a quickly evolving field of science, the patentability requirements are changing, as case law for biotechnological inventions needs to evolve with scientific progress. For the same reason, older case law may already be outdated or become so in the future. *iam*

Table 1. **Statutory patentability of biotechnological subject matter under the EPC 2000**

Patentable subject matter	Non-patentable subject matter
First medical use of a known compound	Inventions whose commercial exploitation would be contrary to "*ordre public*" or morality
Second medical use of a known compound although a first medical use is already known	Plant or animal varieties
Biological material isolated from its natural environment	Methods for treatment of the human or animal body and diagnostic methods practised on the human or animal body
Plants or animals if no varieties are concerned	Processes for cloning human beings
Microbiological processes	Use of embryos for industrial or commercial purposes
An element isolated from the human body or otherwise produced by means of a technical process, including the sequence or partial sequence of a gene, provided that the technical application of the gene is described in the application	Processes for genetically modifying animals which may cause suffering without substantial benefit to man or animal
	The human body or the mere discovery of one of its elements, including the (mere) sequence or partial sequence of a gene

Julia Molitor holds a master's degree in biotechnology, and a postgraduate degree in intellectual property. She previously worked in R&D in different areas of biotechnology (molecular biology, enzymology, microbiology, virology, cell culture, bioprocess engineering) in academia and industry, both in South America and in Europe. Active in the patent field since 2004, she joined E Blum & Co AG in 2006. Fluent in German, English and Spanish, Ms Molitor counsels universities, small and medium-sized companies and international concerns in patent matters, in particular drafting and prosecution of patent applications and supplementary protection certificates.

Julia Molitor
Patent attorney
Email: jmolitor@eblum.ch
Tel: +41 43 222 56 00

E Blum & Co AG
Switzerland
www.eblum.ch

Regula Rüedi studied chemistry and has a PhD in organometallic chemistry. She has several years of practical experience in industry in the fields of analytical chemistry, materials and surface analysis. She became a patent attorney in 1990 and was admitted as a European patent attorney in 1994. Her main activities cover patent law, in particular expert opinions and litigation work in patent infringement and invalidity cases, drafting and prosecution of patent applications and supplementary protection certificates, opposition and appeal procedures, especially in the fields of chemistry, materials, pharmacy, foodstuffs and genetic engineering, as well as advising clients on patent matters.

Regula Rüedi
Partner
Email: rruedi@eblum.ch
Tel: +41 43 222 56 00

E Blum & Co AG
Switzerland
www.eblum.ch