PATENTING OF BIOTECH-INVENTIONS IN EUROPE: NEW DEVELOPMENTS

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Introduction

Now that scientists have completed the sequencing of the entire human genome, new and interesting perspectives are developing with respect to the study of drug action and pharmacogenetics in drug discovery. In the fields of genomics and proteomics, for example, DNA microchip arrays have proved to be useful in the identification of specific gene expression patterns in different tissues or organisms generally, thus allowing a better understanding of cell differentiation and proliferation.

The progress in the fields of molecular biology, biotechnology and molecular medicine since the sequencing of the human genome highlights the importance and potential of these technologies for the pharmaceutical industry. One important way to benefit from these developments is to successfully convert such biotechnological discoveries into patentable inventions in order to obtain an enforceable protective right for potential new compounds, methods or their uses, for example, in treating illnesses or disorders. The steadily increasing number of patent applications in the field of biotechnology at the European Patent Office (EPO) in the past few years reflects the growing significance of biotechnological inventions.

This review will summarise the most relevant recent issues and legal developments under the European Patent Convention (EPC) in the field of biotechnology that are critical for obtaining patent protection in Europe. In particular, we will focus on recent case law established by the Technical Boards of Appeal and the Enlarged Board of Appeal at the EPO.

What is Patentable in Europe?

Patentable Biotech-Inventions (Article 52 EPC)

General

For European patent applications, Article 52(1) of the EPC defines the basic requirements for the patentability of any invention: it must be susceptible of industrial application, must be new, and must involve an inventive step. A further requirement is that the applicant must provide an enabling disclosure which allows the person skilled in the art to carry out the invention (Article 83 EPC).

Of particular interest to those seeking to obtain patent protection for biotechnological inventions are the regulations under Article 52(4) EPC, since this Article excludes from patentability any method of treating humans or animals by surgery or therapy and diagnostic methods practised on humans or animals. The policy behind the exclusion of such methods is grounded in the interest of public health to ensure that those who practise such methods as part of the medical treatment of humans or the veterinary treatment of animals should not be hindered by patents (see T 116/85).[1] In Decision G 5/83,[2] the Enlarged Board of Appeal emphasised that 'the intention of Article 52(4) EPC ... is only to free from restraint non-commercial and non-industrial medical and veterinary activities'. According to several decisions of the Technical Boards of Appeal, an exclusion clause such as the one in Article 52(4) EPC shall be narrowly construed (see, for instance, T 385/86 or T 144/83).[3]

Therapeutic methods

In a recent decision, T 789/96,[4] the Board of Appeal considered the question of whether a method (applied to humans or animals) using a pacemaker and having therapeutic effect was a therapy within the meaning of Article 52(4) EPC. The Board came to the conclusion that the use of such a device having an effect on the heart (within the animal or human body) is, in principle, a method of treatment by applying a therapy. However, in the case at issue, the claimed method was directed to a refinement of technical steps in order to reduce the energy consumption of a pacemaker, which did not have the effect of preventing or treating a pathological condition. The Board noted that the parameters defined by the pacemaker are not used to regulate the amplitude, stimulation frequency or any other value acting directly on the heart. Thus, there is no functional link between the value which is measured and the therapeutic treatment which is applied (see also Decision T 82/93).[5] As a consequence, the Board concluded that

1) T 116/85, OJ EPO 1989, 13, reasons point 3.7.

2) G 5/83, OJ EPO 1985, 64, reasons point 22.

3) T 144/83, OJ EPO 1986, 301, reasons point 3; T 385/86, OJ EPO 1988, 308, reasons point 3.2.

4) T 789/96, OJ EPO 2002, 364.

5) T 82/93, OJ EPO, 1996, 274.

... the use of a pacemaker with a therapeutic effect is not a therapy within the meaning of Article 52(4) EPC if the invention consists in refining said method but the refinement does not have the effect of preventing or treating a pathological condition.[6]

Diagnostic methods

Regarding the patentability of diagnostic methods, the recent Decision T 964/99[7] addresses *inter alia* the question of whether all the steps involved in reaching a medical diagnosis are required to define a diagnostic method, or whether the mere step of sampling a substance from the living human or animal body for diagnostic purposes must be considered a diagnostic method within the meaning of Article 52(4) EPC. In answering this question, the Board considered Decision T 385/86,[8] where it concluded that the only diagnostic methods to be excluded from patent protection were those whose results immediately made it possible to decide on a particular course of medical treatment. A method was therefore considered to be a diagnostic method if it contained all the steps involved in reaching a medical diagnosis. Consequently, those methods providing only interim results may not be diagnostic methods within the meaning of Article 52(4) EPC (1st sentence), even if they can be utilised in making a diagnosis. A restrictive interpretation of this rationale implies that diagnostic methods practised outside the body, such as comparing data with normal values which are based on mental acts, or typical diagnostic procedures practised on the human body such as percussion, auscultation or palpation, could, in principle, be patentable because they do not constitute a complete diagnosis and certainly do not fall within the further medical categories of surgery and therapy. However, in Decision T 964/99, the Board emphasised that the expression 'diagnostic methods practised on the human or animal body' should not be considered to relate to methods containing all the steps involved in reaching a medical diagnosis. Consequently, any sampling of a substance from a body for the purpose of medical examination is considered to be a diagnostic method within the meaning of Article 52(4) EPC.

Surgical methods

Article 52(4) EPC also excludes methods for treatment by surgery on human and animal body. In Decision T 775/97,[9] the Board of Appeal had to decide on a claim submitted by the applicants having the following 'second medical indication' claim format:

> *Use of a [device] for the manufacture of a device for use in a surgical method ...*[10]

The appellant asked whether purpose-related use claims in the second medical use claim format are also applicable to surgical products and functional combinations.

In the Enlarged Board of Appeal Decision G 5/83,[11] it was decided that any claims directed to 'a method of treatment' or 'use of a substance for treatment' are not allowable since such claims contravene Article 52(4) EPC. The Board concluded, however, that any claim directed to 'the use of a substance or composition for the preparation of a pharmaceutical composition' is allowable.

Thus, in Decision T 775/97, the Board of Appeal was obliged to follow the above claim, pointing out that

> *... the reason why claims in the second format of claims ('Swiss type claims') qualify as representing an 'industrial' activity outside the scope of the exclusion from patentability under Article 52(4) EPC is simply the fact that the* ***mere manufacturing of a product,*** *irrespective of whether that product is (also) a 'medicament' because of its capacity to produce certain effects on or in the human or animal body when administered to it,* ***does not necessitate or comprise any action on an individual human or animal body*** *and, therefore, does not constitute a treatment of such body by surgery or therapy. Such treatment would, by definition, require that the product be actually used on an individual human or animal body or bringing about a certain effect on that body; but this is clearly a further and quite different activity of a therapeutical nature because it is directed to the maintenance or restoration of health (e.g. decisions T 19/86,*[12] *T 438/91*[13] *and T 820/92*[14]*). The difference between the two is also exhibited in real life, where the manufacturing and distribution of medicaments is a matter of industry and commerce which is performed by persons who need not and normally do not have a medical qualification, whereas the exercise of therapeutical activities including those involving the treatment by medicaments is reserved for medical practitioners or other persons having a medical knowledge (cf. T 385/86,*[15] *T 24/91*[16] *and T 329/94*[17]*) (emphasis added).*

6) T 789/96, Headnote.
7) T 964/99, OJ EPO, 2002, 4.
8) T 385/86, OJ EPO, 1988, 386.
9) T 775/97, not published in OJ EPO.
10) See T 775/97, claim 29.
11) G 5/83, OJ EPO 1985, 64.
12) T 19/86, OJ EPO 1989, 25.
13) T 438/91, not published in OJ EPO.
14) T 820/92, OJ EPO 1995, 113.
15) Note 8 above.
16) T 24/91, OJ EPO, 1995, 512.
17) T 329/94, OJ EPO, 1998, 241.

Thus, the Board concluded that the use of a known material as starting material for a medical activity is quite different from the use of a known composition for manufacturing a medicament which is otherwise merely an industrial process. Thus, no analogy can be drawn between the use of materials or devices in a surgical method and the use of substances or compositions within the second medical indication. The Board further concluded that no European patent application can be granted with claims directed to a new and even possibly inventive way of using materials or devices like, in this case, endoprotheses, involving treatment by surgery. This would be equally true in the case of product *per se* claims which are typically defined by a construction which is only arrived at in the human or animal body following a surgical step.

A further aspect regarding second medical use claims is that the concept of a second or further medical use can only be applied to claims directed to the use of substances or compositions for the preparation of a medicament intended for use in therapy or therapeutic application. According to Decision T 4/98,[18] the particular illness or disease to be treated with a specified substance or composition must be indicated. The Board of Appeal noted that in the absence of the identification of at least:

(i) the illness or disease to be treated or the ailment to be cured, or
(ii) the nature of the therapeutic compound used for treating or curing the disease, or
(iii) the subject to be treated,

a mere process feature cannot be construed as specifying a particular method of treatment or therapeutic application within the meaning of Article 52(4) EPC.

As a consequence, claims that do not fulfil these requirements must be understood as relating to a non-therapeutic technical activity (process) and therefore assessment of novelty and inventive step has to be done on the basis of this interpretation (see T 4/98, reasons, 8.2 and 8.3).

The requirement of industrial applicability (Article 57 EPC)

According to Article 57 EPC, an invention shall be considered as susceptible of industrial application if it can be made or used in any kind of industry, including agriculture. The question of industrial applicability is particularly important with respect to inventions that concern DNA or protein sequences.

Patenting of DNA and protein sequences

Patent practitioners are often confronted with the question as to whether a mere sequence or partial sequence of a gene is patentable within the meaning of Rule 23e (2) EPC. These sequences can be patentable as long as the industrial application of the sequence of partial sequence is specifically disclosed in the patent application.[19] This means that a concrete technical function must be disclosed somewhere in the patent to satisfy patentability requirements under the EPC.

A decision handed down by an Opposition Division dated 20 June 2001, 'Novel V28 seven transmembrane receptor', addresses this issue.[20] The Opposition Division had to deal *inter alia* with the question of whether a purified and isolated polynucleotide encoding the amino acid sequence of V28 seven transmembrane receptor, or a fragment thereof, possessing at least one ligand/antiligand binding activity or immunological property specific for said V28 seven transmembrane receptor (claim 1), fulfils the requirement for patentability under the EPC. The specification discloses both a genomic and a cDNA clone encoding the V28 protein. Several methods are disclosed that may be used to identify extracellular and intracellular ligands for the V28 protein, however, no specific ligand is disclosed.

The Opposition Division had to decide patentability of this granted patent based on the question of Sufficiency of Disclosure. According to Article 83 EPC, the European patent application must disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. The Opposition Division pointed out that the specification discloses the V28 7TM protein which is predicted but not shown to function as a receptor. The prediction that V28 is a receptor is based on structural elements such as the presence of seven hydrophobic domains separated by hydrophilic domains as well as homologies to known 7TM receptors. The specification does not demonstrate in any way that V28 protein actually is a receptor. Instead, it discloses several methods which can be utilised by the person skilled in the art in order to verify the prediction that V28 protein is indeed a receptor. There might be cases where a predicted function of a protein may be demonstrated in a technically undemanding way such as predicting a specific enzyme activity, in which case the disclosure of the predicted function in combination with a method of verification of said predicted function satisfies the requirements of Sufficiency of Disclosure according to Article 83 EPC. However, the Board noted that the specification of the case at issue does not refer to any group of ligands and thus the skilled person seeking to identify said ligand needs to test a multitude of available candidate compounds using the

18) T 4/98, OJ EPO, 2002, 139.

19) Rule 23e (2) EPC.

20) OJ EPO, 2002, 2930.

described method. This undertaking surely constitutes an undue burden for the skilled person seeking to perform the claimed invention.

For these reasons, the Opposition Division held that the disclosure of the amino acid sequence of the V28 protein and prediction of a function as a receptor in combination with the method disclosed for identification of the respective ligand was not sufficient to disclose a receptor protein.

The patent also included claims that related to an antibody substance specific for V28 protein without such antibody substance being specifically disclosed. The Opposition Division held that the generation of these antibodies is not considered to be a routine matter because of the labour-intensive exclusion of cross-reactivity of the candidate specific antibody with any other protein. Therefore, the identification of specific antibodies suitable for counteracting a speculative activity of V28 protein, that is, induction of inflammation, is not enabled by the disclosure of the specification.

Similarly, the Opposition Division concluded that since no antagonists of V28 protein are disclosed in an *in vitro* method, the use of an agonist or antagonist of the V28 protein is not sufficiently disclosed.

The requirement that patents are granted only for inventions which are suitable for industrial application (Article 57 EPC) is further explained in Rule 23e (3) EPC. This indicates that the industrial application of a sequence or a partial sequence of a gene must be disclosed in the patent application.

In case of the V28 seven transmembrane receptor, the Opposition Division held that no function of the claimed protein is disclosed. Potential uses of the invention are disclosed in the specification, which are based on a proposed function of the V28 protein as a receptor that was not supported by the description. Thus, the potential uses disclosed in the patent application are speculative, that is, they are not specific, substantial and credible so as to meet the standard for an industrial application.

The case described above of the V28 seven transmembrane receptor shows that the proposal of an activity or function of a nucleic acid or protein should be credibly shown in the examples, and that at least one way should clearly be indicated of enabling the person skilled in the art to carry out the claimed invention. It also follows from this case that a mere laundry list disclosed in the patent specification summarising speculative functions of a protein is not in itself a reliable basis for recognising the industrial application of this protein. In order to fulfil the requirement of industrial applicability for biotechnological inventions, it is not sufficient for the specification simply to show that a protein or nucleic acid sequence can be made and used. Therefore, the disclosure of the function of a nucleic acid and/or protein is and remains a basic requirement for obtaining patent protection for nucleic acid or protein sequences in Europe.

Patenting of Expressed Sequence Tags (ESTs)

Within the European patent community, there has been controversy regarding patentability of Expressed Sequence Tags (ESTs) in the last few years. ESTs are partial sequences which are derived from complementary DNA (cDNA) clones. They are generated by the sequencing of either one or both ends of an expressed gene. ESTs have applications in the discovery of new human genes, mapping the human genome, and identifying coding regions in genomic sequences. The problem underlying the patenting of ESTs is that they are sequences with an unknown function. The only credible function is their use as a probe for screening libraries, identifying nucleotide sequences, and mapping their position within a genome. However, only one sequence per patent application would be patentable due to the unity requirements of Article 82 EPC as long as they are not linked by a single general inventive concept. In conclusion, even though there is no explicit case law concerning the patentability of ESTs, it is generally accepted that ESTs are not patentable in Europe as long as their functions are credibly disclosed in order to fulfil the requirements for industrial application (Article 57 EPC).

Exceptions to Patentability (Article 53 EPC)

Article 53(a) EPC indicates that European patents shall not be granted for inventions of which publication or exploitation would be contrary to *ordre public* or morality. In Decision T 356/93,[21] it is stated that the concept of *ordre public* covers the protection of public security and the physical integrity of individuals as part of society (see T 356/93, reasons, 5). This concept also encompasses environmental protection. Accordingly, under Article 53(a) EPC, the exploitation of inventions which are likely to breach public peace or social order, or to seriously prejudice the environment are excluded from patentability as being contrary to *ordre public*. However, the Board emphasised that approval or disapproval of the exploitation by national law(s) or regulation(s) does not constitute *per se* a sufficient criterion for the purposes of examination under Article 53(a) EPC.

According to Rule 23d EPC, the following European patents shall not be granted which, in particular, concern:

(a) processes for cloning human beings;
(b processes for modifying the germ line genetic identity of human beings;
(c) uses of embryos for industrial or commercial purposes; and

21) T 356/93, OJ 1995, 545.

(d) processes for modifying the genetic identity of animals which are likely to cause them suffering without any substantial medical benefit to man or animal, and also animals resulting from such processes.

As far as the human body or its elements are concerned, the legislative intention clearly excludes from patentability the human body at various stages of its formation and development, and the simple discovery of any of its elements, including the sequence or partial sequence of a gene.[22] On the other hand, 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 may constitute a patentable invention even if the structure of that element is identical to that of a natural element.[23]

Patenting of plant or animal varieties

According to Article 53(b) EPC, plant or animal varieties or essentially biological processes for the production of plants or animals are also excluded from patentability, whereas microbiological processes or the products thereof are not.

On 20 December 1999 the Enlarged Board of Appeal decided Case G 1/98 (*Transgenic plant/Novartis II*).[24] The Enlarged Board of Appeal held that a claim directed to transgenic plants may not be excluded from patentability in view of Article 53(b) EPC, even if plant varieties fall within the scope of the claim.

This is now also evident from Rule 23c (c) EPC, which states that inventions are patentable if they concern plants or animals if the technical feasibility of the invention is not confined to a particular plant or animal variety.

Patenting of embryonic stem cells

Rule 23d (c) EPC defines which inventions are for morality reasons excluded from patentability (Article 53a EPC) and provides that human embryos for industrial or commercial purposes shall not be patented.

According to established case law, exceptions to patentability must be narrowly construed.[25] According to the Guidelines for Examination in the EPO, Chapter IV, 3.1:

> *a fair test to apply is to consider whether it is probable that the public in general would regard the invention as so abhorrent that the grant of patent rights would be inconceivable.*

Rule 23d (c) EPC leaves open the question of what is exactly excluded. For example, what is encompassed by the term 'embryo' in Rule 23d (c) EPC? A further question is whether cells obtained from embryos or processes involving human stem cells are also excluded.

According to Rule 23b (1) EPC, the Directive 98/44/EC of 6 July 1998 on the legal protection of biotechnological inventions shall be used as a supplementary means of interpretation. Article 7 of the Directive states that the European Group on Ethics (EGE) is charged with the general evaluation of the ethical aspects of biotechnology.

On 7 May 2002, the EGE released Opinion no.16 on the ethical aspects of patenting inventions involving human stem cells. It is the opinion of the EGE that:

– Isolated stem cells which have not been modified do not, as product, fulfil the legal requirements of patentability;
– Only stem cell lines which have been modified by *in vitro* treatments or genetically modified so that they have acquired characteristics for specific industrial application, fulfil the legal requirements for patentability;
– As to the patentability of processes involving human stem cells, whatever their source, there is no specific ethical obstacle, in so far as they fulfil the requirements of patentability (novelty, inventive step and industrial application).

This means that processes which involve human stem cells, for example as starting material, should not be excluded from patentability for morality reasons alone. Regarding product claims to human stem cell lines, the EGE recommends that patent protection should only be possible for modified or specific differentiated stem cell lines for specific therapeutic or other uses. Furthermore, the EGE holds the view that applicants should declare the source of human stem cells described in an application. In addition, the view is expressed that patents should only be granted when the patent claims (product claims) refer to a specific and sufficiently accurately described stem cell line.

It remains to be seen whether or not the EPO will deal with patent applications in this field according to the guidance provided by the EGE.

Allowability of disclaimers at the EPO

The question of admissibility of the introduction of a disclaimer at the EPO has been controversial and has been referred to the Enlarged Board of Appeal (cf. T 451/99[26] and T 507/99[27]). The Enlarged Board of Appeal will have to decide in the two respective pending decisions, G 1/03[28] and G 2/03,[29] whether the introduction of a disclaimer into a

22) Rule 23e (1) EPC.

23) Rule 23e (2) EPC.

24) G 1/98, OJ EPO, 2000, 111.

25) See Case Law of the Board of Appeal, 4th edn, at 32.

26) T 451/99, OJ EPO, 2003, 334.

27) T 507/99, OJ EPO. 2003, 225.

28) G 1/03 pending case to T 507/99.

patent claim is admissible within the ratio legis of Article 123 (2) EPC even in the absence of explicit support in the application as originally filed. According to Article 123 (2) EPC, a European patent application may not be amended in such a way that it contains subject matter which extends beyond the content of the application as originally filed. For example. in decisions T 426/94[30] and T 934/97[31] of the Technical Board of Appeals, it was noted that the prior art which the disclaimer excludes must be accidentally novelty-destroying prior art. A disclaimer introduced in order to establish novelty should exclude precisely that subject matter which is disclosed in the prior art. In decision T 351/98,[32] the Board of Appeal reflected the interpretation that in case an overlap occurs between prior art that falls under Article 54(3) EPC (elder European right) and the claimed subject matter, a disclaimer may be admissible under Article 123(2) EPC. On the other hand, the decision T 323/97[33] stated principles which are expressly in contrast to the established case law. Accordingly, a disclaimer may not be introduced into a claim to meet an objection due to lack of novelty when the specification as originally filed provides no support for the disclaimer. The introduction of a disclaimer would therefore contravene the requirements pursuant to Article 123(2) EPC.

The outcome of the pending decisions G 1/03 (referral decision T 507/99) and G 2/03 (referral decision T 451/99) of the Enlarged Board of Appeal will clarify the matter of admissibility of disclaimers at the EPO.

29) G 2/03 pending case to T451/99.

30) T 426/94, not published in OJ EPO.

31) T934/97, not published in OJ EPO.

32) T 351/98, not published in OJ EPO.

33) T 323/97, not published in OJ EPO.