Protecting and Enforcing Life Science Inventions in Europe

under EPC and EU Law - From Antibodies to Zebrafish

von
Dr. rer. nat. Franz-Josef Zimmer, Steven M. Zeman, Steven Zeman, Dr. Jens Hammer, Dr.-Ing. Klara Goldbach, Dr. Bernd Allekotte

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D.III.2.b. Morality and "ordre public"

According to Art. 53(a) EPC, inventions the commercial exploitation of which would be contrary to "ordre public" or morality, are excluded from patent protection. To our knowledge, there is no decision discussing the allowability of a protein under Art. 53(a) EPC. However, the same criterion applies for proteins as for any other subject-matter; as stated in the Guidelines (G-II,4.1):

> 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. If it is clear that this is the case, an objection should be raised under Art. 53(a); otherwise not.

D.III.2.c. Methods of treatment

According to Art. 53(c) EPC, methods for the treatment of the human or animal body by surgery or therapy and diagnostic methods practised on the human or animal body are exceptions to patentability.

The case underlying **T 820/92 (Contraceptive method/THE GENERAL HOSPITAL)** claimed a method for preventing pregnancy in female mammals, comprising the administration of LHRH and steroid hormones. The LHRH component was the main contraceptive ingredient, and the steroids served to correct any biological functions adversely effected by the LHRH. The Appellant argued that the method as a whole is a contraceptive method which is not excluded by Art. 52(4) EPC 1973 (now Art. 53(c) EPC). The Board, however, held:

> This argument is based on a misconception of the nature of the prohibition of Article 52(4) EPC. By providing that methods for treatment of the human or animal body by surgery or therapy and diagnostic methods practised on the human or animal body shall not be regarded as inventions which are susceptible of industrial application, the first sentence of Article 52(4) EPC creates an exclusion from patentability that has been consistently interpreted by the EPO Boards of appeal as meaning that such a method cannot be the subject-matter or part of the subject-matter covered by a claim. (point 5.3)

The claimed method was thus not allowable due to the therapeutic/prophylactic aspect of simultaneously administering steroids. The application of proteins outside of the human body, e.g. for performing diagnosis on a tissue sample, is generally not in conflict with Art. 53(c) EPC (Art. 52(4) EPC 1973).

D.III.2.d. Novelty

In **T 269/87 (Prochymosin/CELLTECH)**, an Appeal Board considered whether the disclosure of a DNA coding for the protein prochymosin (another name for prorennin) including the information on the sequence of the active (mature) protein chymosin, would anticipate the disclosure of a process for preparing chymosin involving cleavage of prochymosin, yielding the active, mature protein. The Board held:

> The cleavage of the prochymosin protein, however, to chymosin is neither directly expressed nor unequivocally implied in the disclosure of document (1). The chapter on the ex-

pression of "methionine-prorennin" is silent on any further steps […]. Any implied cleavage, in terms of "activation", relates to other proteins […]. The reference to the nucleotides responsible for the formation of the inactive "zymogen" part of rennin (chymosin) […] which "is removed" to generate active rennins, is no disclosure of the specific cleavage step claimed in the present case, but relates to the DNA level. Document (1) is, therefore, ineffectual in destroying the novelty of claims A1 or A2 under Article 54(3) EPC, irrespective of its own priority rights. (point 15)

Therefore, in this particular case, a disclosure allowing one to deduce the structure of the mature protein, without explicitly providing it, was not considered to be novelty-destroying for the process of preparing the mature protein as such.

In **T 877/90 (T-cell growth factor/HOOPER)**, a Board of Appeal examined the novelty of a T-cell growth factor which was characterized as being serum-free and mitogen-free. The Board found that the closest prior art document discloses a T-cell growth factor which was not mitogen- and serum-free and consequently acknowledged the novelty of the claimed subject-matter.

This appears to be the first decision in the field of biotechnology in which novelty of a substance is established by a higher degree of purity compared to a known product. In order to put the results of **T 877/90** in the correct perspective, one should compare the conclusion from **T 877/90** with that of earlier decision **T 205/83 (Vinyl ester/crotonic acid copolymers/HOECHST)**. In **T 205/83**, it was held that a known product does not necessarily acquire novelty merely by virtue of the fact that it is produced in pure form (point 3.2 of the decision). Although in the decision the possibility of establishing novelty by higher purity was not definitely excluded, it was the previous practice of the EPO not to accept novelty of a protein differing from the prior art only by improved purity. As a consequence of **T 877/90**, this practice may be changing. Indeed, this practice was confirmed by **T 90/03 (Phytase/BASF)**. For the field of small molecules, the situation may be different as e.g. decided in **T 990/96 (Erythro-compounds/NOVARTIS)** where the Board did not accept the degree of purity as a feature for establishing novelty.

In **T 158/91 (Human growth hormone/GENENTECH)**, an Appeal Board confirmed established case law according to which a prepublished teaching can only defeat novelty if it enables a person skilled in the art to reproduce its teaching. The Board held:

Certainly, the question of sufficient disclosure, be it of a prior art document or a patent application in question, has to be examined in each case on its own merits. An examination as to the sufficiency of a disclosure depends on the correlation of the facts of the case to certain general parameters.

These parameters are for example:

(a) the character of the technical field and the average amount of effort necessary to put into practice a certain written disclosure in that technical field;
(b) the time when the disclosure was presented to the public and the corresponding common general knowledge;
(c) the amount of reliable technical details disclosed in a document. (point 2.3)

In **T 886/91 (Hepatitis B virus/BIOGEN INC.)**, one of the Opponents submitted that small differences in the claimed sequence compared to a known sequence are not sufficient to confer novelty to the claimed sequence. The Board did not accept this argument, since

> it is well known that even a change in one amino acid can dramatically change the properties of a protein molecule. (point 8.1.2)

Further, one of the Opponents argued that there were common identical stretches in the claimed sequences and the known sequences and thus the claimed sequences should lack novelty. The Board held that this is

> merely theoretical because none of the cited documents discloses or suggests any discrete fragments of the reported sequences as an identifiable entity which could be used for a comparison. (point 8.1.2)

In **T 223/92 (HIF-Gamma/GENENTECH)** two aspects are noteworthy.

Claim 1 of the patent in question reads as follows:

> Human immune interferon of the amino acid sequence depicted in Figure 5 hereof and alleles thereof, free from other protein with which it is ordinarily associated.

According to Figure 5, the amino acid sequence comprises about 146 amino acids, allowing calculation of the molecular weight as 17400 D.

After the priority date it was discovered that IFN-γ often occurs as a dimer or trimer. An Opponent argued that one of the prior art documents, document (21), may have described a glycosylated dimer. The Board stated:

> This may or may not be the case, but it was not possible for the skilled man at the time of priority to recognise this. What was available to the public within the meaning of Article 54(2) EPC by document (21) was the information that in a culture fluid of induced lymphocytes after certain purification steps a protein is contained that has properties differing from those of the well characterised interferon-alpha and interferon-beta and has a molecular weight of 58000. (point 4.3)

Moreover, the Board considered document (21) not to be novelty destroying for the following reason:

> [A]t the priority date neither the monomer, nor any oligomer was available as such, but merely infinitesimal amounts of something that included a compound showing activity typical of interferon gamma. (point 4.4)

Therefore, if only the activity of a certain protein is known from the prior art that does not describe a reproducible way of obtaining more than "infinitesimal amounts" of the protein having the activity, this disclosure might not be sufficient to defeat novelty.

In **T 412/93 (Erythropoietin/KIRIN-AMGEN)** an Appeal Board confirmed the following established principle:

> [T]he fact that a product is referred to in a claim as being the result of some process, does not automatically mean that the product is novel even if it is beyond dispute that the process referred to is new. The purpose of the reference to the process was to exclude those products

which in the prior art were not obtained by the process. If, on the evidence available, the process appears capable of producing every product meeting the characteristics of the product of the prior art, the reference to the process is not a limitation for the purpose of considering novelty. The process feature in a product claim can only be relied on for establishing novelty over the prior art, where use of that process necessarily means that the product has a particular characteristic and the skilled person following the teaching of the specification would inevitably achieve that characteristic, would be aware of that characteristic and would discard any products not having it. (point 33)

In this case, the Patentee had attempted to distinguish recombinant erythropoietin over known urinary erythropoietin. The Board held that recombinant erythropoietin may not necessarily be different from urinary erythropoietin.

The Board finally accepted a claim reciting the erythropoietin to be the product of eukaryotic expression of an exogenous DNA sequence and having a higher molecular weight by SDS-PAGE than erythropoietin isolated from urinary sources.

In **T 656/94 (Colony-stimulating factor/KIRIN-AMGEN)** the Opponent-Appellant argued for a lack of novelty of the patent underlying the decision claiming *inter alia* in claim 1 of the main request:

An isolated polypeptide consisting only of part or all of the amino acid sequence 1–174 set forth in Table VII which: […]:

In the Board's view it was clearly shown that the prior art documents disclosed a mixture of polypeptides having 174 and 177 amino acids in a molar ratio of 80:20, wherein the 177 amino acid polypeptide is a splice product with 3 additional amino acids inserted. The present invention, however, according to the Board, was directed to a single species, which was made clear by the features "isolated" and "only" in claim 1. Therefore, the Board held that the mixture disclosed in the prior art was not novelty-destroying for the present invention.

The above case is one of the rare examples where the term "isolated" actually helped the Applicant to overcome the prior art. As a rule of thumb, the term "isolated" should be avoided, as in most cases it does not help to overcome prior art.

In **T 367/95 (Antihemophilic factor/PHARMACIA)**, the underlying patent was revoked by the Opposition Division for lack of novelty. Claim 1 was directed to a fragment of Factor VIII:C further characterized by molecular weight, partial amino acid sequences and amino acid composition. In considering the prior art the Board pointed out that merely conjectural statements, such as "may be required", "seem to be", or "presumably" were not sufficient to clearly and unmistakably disclose the claimed features and thereby anticipate the claimed subject-matter. Furthermore, the Board stated that amino acid composition data was suitable to establish novelty and that any argument to the contrary based on experimental error needed to be substantiated.

In case **T 429/96 (Serine protease inhibitors/AMGEN)**, the Board had to decide on the novelty of a claim directed to a purified serine protease inhibitor consisting of a single unfragmented polypeptide chain, the inhibitor being

characterized by an amino acid sequence. The relevant prior art disclosed a composition containing the claimed inhibitor in degraded form as a mixture of fragments. The Board found the claim directed to the undegraded polypeptide chain to be novel over the mixture of degraded protein fragments.

In **T 1147/98 (Cartilage-inducing factor/CELTRIX PHARMACEUTICALS INC.)**, the appeal lay from the Opposition Division's decision to revoke the patent. On appeal, the Patentee filed new claims directed to a "homogenous" protein. Since the cited prior art documents disclosed a mixture of different relevant biochemical activities, the Board held that a "homogenous" protein was not disclosed by a mixture, and hence the claims filed on appeal were novel. (See similar finding in **T 656/94** above).

In **T 522/99 (Soybean desaturase/DU PONT)**, the Board had to decide on the novelty of a claim with product-by-process character. Claim 6 of the main request was directed to a

> [r]ecombinant non-fused VP1 protein, […], formed in Spodoptera frugiperda cells according to claim 3.

The Board held this claim as anticipated over a document disclosing the expression of the VP1 protein in Chinese hamster ovarian cells, thereby confirming established case law, which requires that a product defined by its production process must fulfill the patentability requirements by itself. The production process can only be considered as a limiting feature in as far as it confers particular characteristics on the product not found in the prior art.

In **T 881/01 (Alpha-amylase reagent/MODROVICH I.E.)**, the Opposition Division used technical features only disclosed in the specification to delimit the claimed subject-matter from the prior art. The Board criticized this claim interpretation and stated:

> While it is true that Article 69(1) EPC second sentence states that the description and drawings shall be used to interpret the claims, this does not make it legitimate to read into the claim features appearing only in the description and then relying on such features to provide a distinction over prior art. This would not be to interpret claims but to rewrite them. The preparatory material available on the discussions leading up to the European Patent Convention, shows that the effect of Article 69 EPC and its Protocol on Interpretation was always only considered in relation to extending the extent of protection conferred beyond the strict literal meaning of the terms of the claims, and never for excluding what on the clear meaning was covered by the terms of the claims. (point 2.1)

In **T 1080/01 (Thermostable enzyme/F. HOFFMANN-LA ROCHE)**, it was argued that multiple prior art documents implicitly disclosed the claimed polymerase by means of disclosing a process that, when strictly followed, would result in the claimed protein. In this regard the Board held:

> A faithful reproduction of an experiment reported in any of documents (3), (9) and (10) can only be one which reproduces as accurately as possible the very same experimental conditions the authors were using, starting from the very same material. The only deviations which may be acceptable should be those resulting from the replacement of a material which no longer exists, provided that those deviations can be proven not to have any influence at all

on the outcome of the reproduced experiment. Deviations made only for experimental convenience are not acceptable. (point 54)

Since none of the submitted documents fulfilled the criterion of accurate reproduction of the disclosed processes according to the patent, the Board did not see it proven beyond reasonable doubt that the disclosed processes in the prior art would inevitably result in the claimed product, i.e. the polymerase.

In **T 1120/01 (Cell surface antigen/OSAKA BIOSCIENCE)**, the Examining Division refused the underlying patent application *inter alia* for lack of novelty of a product claim directed to a protein. On appeal, however, the Appeal Board found that none of the cited prior art documents provided an enabling disclosure of the claimed protein, since they either failed to disclose all information necessary for the disclosed purification of the protein, or they did not disclose any purification at all. Therefore, the cited documents were not considered to anticipate the claimed protein.

In **T 90/03 (Phytase/BASF)**, the Board discussed the role of a protein preparation's purity for establishing novelty. The Board emphasized that in this regard low molecular weight compounds and high molecular weight proteins cannot be treated equally. While methods of purification of small organic molecules are common general knowledge of the skilled person, the purification of proteins is far from being standardized. In considering previous case law, the Board concluded that even though the present claims also differed from the prior art by additional technical features, the degree of purity alone would be sufficient to establish novelty (see also **T877/90** discussed above).

In **T 1303/04 (Myelin basic protein/UNIVERSITY OF ALBERTA)**, the Board emphasized once more:

> [I]t is not justifiable to decide whether a document is prejudicial to novelty on the **basis of probability or plausibility**. In order to decide that the subject-matter of a claim lacks novelty, the department concerned, having taken all facts and arguments put forward during the proceedings into consideration, has to be **sure** that the decision is justified. (point 6)

In **T 1010/05 (Protein hydrolysate/VALIO)**, a method step of the process used to define a product (product-by-process) was considered to differentiate the claimed product ("hydrolysate") from the prior art ("yoghurt"). In particular, the process step of hydrolysis by pepsin and/or trypsin was considered to confer structural characteristics on the claimed "hydrolysate". These characteristics were not proven to be disclosed in the prior art, since it was not shown that these proteases or other proteases with the same cleavage characteristics were present in the prior art "yoghurt".

In **T 1414/05 (MHC complexes/SUNOL)**, the implicit structural characteristics of a functional feature helped to establish novelty over the prior art. The claimed MHC complex in question was limited by the feature "capable of modulating the activity of a T-cell receptor to induce T-cell proliferation". In contrast, the prior art disclosed MHC complexes, which suppressed T-cell proliferation. The question was whether in the absence of any other differentiating

features, the MHC complexes of the prior art would also be suitable to induce T-cell proliferation. To address this question, the Appellant submitted that for fulfilling the claimed function the peptide presented by the MHC molecule must be properly positioned, therefore giving the functional feature a structural implication. Based on this argument, the Board held that the suppressing MHC complex of the prior art would not be able to induce T-cell proliferation as required by the invention and that, therefore, the MHC complexes of the prior art were different from the claimed molecules.

In **T 847/07 (Factor VIII formulation/BIOVITRUM)**, a pharmaceutical formulation was claimed as "suitable for subcutaneous, intramuscular or intradermal administration". Regarding the limiting effect of this claim element, the Appeal Board held:

> Claim 1 has to be construed as relating to formulations that may be used for any form of administration as long as they are also suitable for subcutaneous, intramuscular or intradermal administration.
>
> In the Board's view the term "suitable for subcutaneous, intramuscular or intradermal administration" does however limit the meaning of the claim in so far as it excludes preparations which are not suitable for these forms of administration, such as preparations containing potentially toxic constituents or inactive factor VIII. (point 8)

Since the Respondent, however, acknowledged that the formulations of the prior art would be suitable for the above mentioned forms of administrations (even though not explicitly disclosed), and in the absence of any other limiting technical features, the Board denied novelty for the claimed subject-matter.

In **T 1898/07 (Interferon Formulations/BIOGEN)**, the Board emphasized once again (see also **T 1010/05** above) that a product-by-process claim is only patentable if the product itself fulfills the patentability requirements. The claim in this case was directed to a liquid composition. In addition to process features, the claimed liquid composition was further defined, *inter alia,* by the features: i) is contained in a syringe and ii) wherein the syringe is contained in a package. The Board held that these features do not constitute technical features describing the claimed liquid composition but merely describe the package, which contains the liquid composition. Therefore, the Board did not consider these features for the assessment of novelty.

D.III.2.e. Inventive step

T 181/88 (Assaying reagent/UNITIKA LTD.) concerns an Applicant's appeal against the decision of an Examining Division to refuse an application having the following main claim:

> A cholinesterase-assaying reagent comprising:
> acetylcholine;
> a thermostable acetate kinase; and
> adenosine triphosphate.

The Examining Division denied an inventive step of the claimed reagent, on the basis that reagents differing from claim 1 only in the use of a non-thermostable enzyme were already described in a first document, and a second document disclosed a thermostable acetate kinase, which from a third document was known to have "high residual activity".

The Appeal Board reversed the decision of the first instance, since there was no indication in the prior art that the assaying reagent could be improved by including a thermostable enzyme. Moreover, there was no incentive to use a thermostable enzyme, since no single step of the complex reaction was conducted under heat stress, but instead at 37°C or room temperature. Thus, the Board did not agree that replacing the conventional acetate kinase by a thermostable enzyme was obvious.

T 249/88 (Milk production/MONSANTO) concerned an appeal against the refusal of an application by an Examining Division. The claim in dispute was directed to a method for increasing the milk production of a cow by administering recombinant bovine growth hormone (bGH) including an N-terminal methionine, which is not present in natural pituitary derived bGH. The relevant prior art taught methods for increasing the milk production of a cow by administering natural (pituitary derived) growth hormone and suggested the administration of recombinant bGH, which was known from a further document. In addition, it was known that an N-terminal methionine did not affect the biological activity of human growth hormone. The Board confirmed the refusal of the application by the first instance, holding that the skilled person, in view of the cited prior art, would have considered the claimed method as an improvement of the teaching of the closest prior art documents. The Board thus concluded:

> [A] person skilled in the art *would* indeed have administered the available form of recombinant bGH, i.e. the N-Met-bGH obtained according to GB-A- 1 565 190, without any modification to a cow in the reasonable expectation of obtaining the same or even a greater increase in milk production as observed when natural (pituitary derived) bGH is administered. (point 7.6)

In response to the Proprietor's argument that a person skilled in the art would not have been able to *predict* that N-Met-bGH would increase the milk production of a cow on the basis of the cited prior art, the Board held:

> The necessity of experimentally confirming a reasonably expected result does not render an invention unobvious. Absolute predictability, especially in the field of biologically active chemical compounds, is rather exceptional, but inventions relating to such compounds and their administration to living organism may nevertheless be obvious. However, if such administration were to lead to unexpected results, which is not the case here, this may provide a basis for demonstrating unobviousness. (point 8)

In **T 60/89 (Fusion proteins/HARVARD)**, an Appeal Board established that the same level of skill had to be applied when considering, for the same invention, the two questions of sufficient disclosure and inventive step (point 3.2.5 of the decision). The Board further noted: