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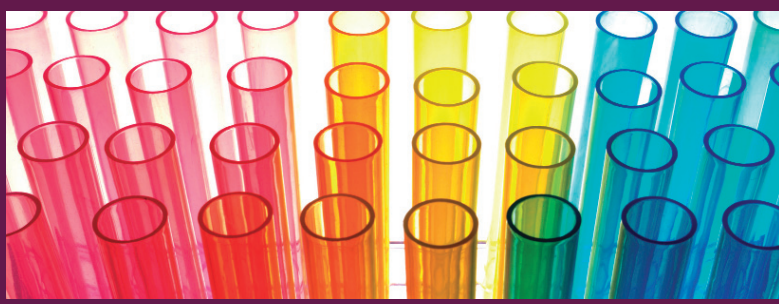

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PATENTING PROTEIN PHARMACEUTICALS IN EUROPE

VALEA

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Patenting protein pharmaceuticals in Europe

Treatment methods based on biotechnology are becoming increasingly important in the life sciences industries. **Ylva Skoglösa** and **Annika Unge** of **Valea** examine how the EPO treats protein pharmaceuticals

Besides the classical medically active substances (the so-called small molecules), novel treatment methods based on biotechnology are increasingly gaining in importance for industry and patient care. These methods include biopharmaceuticals and biosimilars, therapeutic antibodies, gene and cell therapy, regenerative medicine, tissue engineering and nanoscale medicine transporters.

Introducing protein pharmaceuticals

Protein pharmaceuticals form a rapidly growing category in the arsenal of drugs. Many natural proteins are being used to treat diabetes, anaemia, hepatitis and cancer. What is more, already approved protein pharmaceuticals are being modified to improve their effectiveness. There are now more than 200 approved peptide and protein pharmaceuticals on the FDA list.

Classic examples of protein and peptide pharmaceuticals are:

- Insulin (diabetes)
- Interferon ß (relapsing MS)
- Interferon γ (granulomatous)
- TPA (heart attack)
- Albumin (hypovolemia/hypoalbuminemia)
- HGH (growth disturbance)
- Factor VIII (haemophilia)
- Erythropoietin (anaemia)
- Calcitonin (enhance bone mass)
- Oxytocin (stimulate labour)
- Vasopressin (antidiuretic)

The rapid growth in the understanding of biological processes based on the last decade's research in the genome and the proteome projects has contributed to a more thorough understanding of the function of biomedical substances. Modern biotechnology also gives researchers the possibility to generate and to investigate broad libraries of substances, greatly simplifying the identification of candidate substances from naturally occurring proteins and peptides.

Challenges for the patent system

As for any pharmaceutical substance, obtaining patent protection for these new protein-based drugs is important. However, in several aspects, the patent system is largely oriented towards the needs and parameters of classical small molecule pharmaceuticals, whereas the requirements for patent protection for biological macromolecules differs from the protection for more easily definable chemical entities.

Optimally for patent protection, a discovered protein or peptide is novel: it has never been isolated and disclosed. Then, even if the protein or peptide is a naturally occurring protein or peptide, it is possible to obtain patent protection for the substance *per se*, as long as the protein or peptide has previously not been characterised, and provided the protein or peptide has an industrial application. Hence it is not possible to obtain protection by just listing amino acid sequences without any information about their industrial application. Support for the technical effect of the protein or peptide, including that demonstrated by way of examples, is required in the application. The requirements for proof-of-concept are steadily increasing at the European Patent Office, more or less in parallel with the increasing understanding of biological processes in the field. Laboratory techniques – the results of which are commonly used to establish inventive step over the prior art – are already deemed to have become standard laboratory practice. Inventive step then becomes a question of whether or not there is any incentive for the skilled artisan.

Today, new proteins or peptides are often identified via their amino acid sequences. A novel protein may therefore be claimed by its amino acid sequence. However, in analogy with T12/81 in the field of chemistry, even if it has not been possible to sequence the protein or peptide, patent protection may be obtained by defining the protein or peptide via physical parameters, such as chromatography profiles and molecular mass or by the way the protein is isolated (that is, by product-by-process claims).

The oft-preferred identification of a protein or a peptide via its amino acid sequence, however, leads to the delicate problem of how to present this sequence to obtain patent protection that actually corresponds to the invention's contribution to the art (in line with the teachings of T409/91 and T435/91). For instance, the amino acid sequences of many naturally occurring proteins are to a large degree made up of pharmaceutically uninteresting parts, whereas only a small part of the protein is directly involved in its actual biological activity, for example forming the binding pocket of an enzyme or the epitope of an antigen. Those active parts of a protein often tend to be conserved between proteins from different species, while other parts of the protein may be more varied. For example, amelogenins, the major constituents of the enamel matrix of developing teeth, are a family of proteins that are highly conserved through vertebrate evolution and demonstrate a high overall level of sequence homology among all higher vertebrates examined (80%). Thus, an approximate 4% difference in amino acid sequence from Homo sapiens amelogenin to porcine amelogenin does not seem to relate to its biological activity in either of the animals. Actually, the human body still recognises the pig's protein as its own.

Even in the active site of a protein, not all amino acids may be absolutely necessary for the protein's biological activity, and some amino acids may easily be substituted by similar or completely different amino acids, without the loss of biological activity.

Limiting a patent claim to a specific amino acid sequence therefore provides very narrow protection for the protein or peptide; protection which can easily be circumvented by third parties by the substitution of one or more of the amino acids which are not absolutely necessary for biological activity. Rather, the protein or peptide is preferably identified in a more open manner as for example "comprising" the amino acid sequence or as having a certain degree of homology or identity to the sequence. Interestingly, in T762/07, "identity" was interpreted as narrower than "homology".

Inventive step

In classical chemistry, such as T852/91, it is established that to deny inventive step for novel chemical compounds because of their structural similarity to known chemical compounds amounts to an allegation that a skilled person would have reasonably expected the same or similar usefulness of both the known and the novel compounds as the means for solving the technical problem underlying the application in question. Such an expectation would be justified if the skilled person knew that the existing structural differences of the chemical compounds concerned were so small that they would have no essential bearing on those properties, which where important for solving the technical problem and could be disregarded. In other words, a chemical entity can be new and inventive even if the changes in the chemical structure are minimal.

T643/96 ruled that, in the field of classical drug design, any structural modification of a pharmacologically active substance is, in the absence of an established correlation between structural feature and activity, expected *a priori* to disturb the pharmacological activity profile of the compound. For the reasons described above, this should not reasonably be applied directly to protein pharmaceuticals. However, the EPO unfortunately tends towards granting patents with a very narrow scope with regard to the degree of identity required, relying too heavily on case law concerning classical small molecule chemistry.

What is more, the need for a broad scope of sequence identity stands in direct contrast to the need for the technical effect to be reproducible across the whole scope of the claims, for the invention to have inventive step as ruled in T2/83 and in T939/92. Thus, although a claim directed to an amino acid sequence being at least 80% identical to human amelogenin will invariably encompass proteins that do not possess enamel matrix activity, limiting the claims to amino acid sequences being at least 99% identical to human amelogenin still can hold such false positives, depending on exactly which amino acids differ. On the other hand, a claim limited to a 99% identity will exclude the porcine amelogenin protein, which is actually proven to promote dental regeneration in humans.

An applicant trying to patent a protein thereby becomes trapped between trying to obtain reasonably broad protection to hinder competitors from circumventing the patent all too easily, while still protecting a protein or peptide which actually has the desired biological activity. A claim scope that is too broad will almost inevitably lead to a rejection based on insufficient disclosure of the invention.

A possible solution to this conundrum is to define the protein through an identity of a reasonably broad percentage with its amino acid sequence in combination with a further technical effect, such as a desired biological effect, or a chemical or physical property. In analogy to the ruling in T723/05, as long as reasonably closed language is used in a claim, the technical effect is considered to be a limiting characteristic of a given substance. In T857/06, the denotation of the protein as a "Tumor Necrosis Factor Binding Protein II" in combination with data on the characteristics of the protein in the description was important for distinguishing this protein from prior art. Nonetheless, it is essential for this strategy to include an easy and detailed test in the description, so that the person skilled in the art, who all of a sudden is no longer able to execute the new standard laboratory protocols routinely, can count on a reasonable expectation of success (see T2/83). In addition, one needs to be aware of the imperative for the validity of any priority claim that no amino acid residues in the sequence as filed are changed, even if inventors wish to

introduce minor and biologically insignificant corrections to the original listing during the priority year.

Fall-back positions

As patent applications for protein-based drugs are often filed early in the research process, when it is not yet clear exactly which amino acid sequence the pharmaceutical compound of choice will have, it is important to define the amino acid sequence of the protein or peptide broadly, while still ensuring that the application recites more specific amino acid sequences of preferred embodiments as fall-back positions. It is unnecessary to say that a fall-back on to such severely limited product claims does not in many cases result in a satisfactory scope of protection for the inventors. On the other hand, the research is often focused on trying to identify the biologically active parts of the protein to be able to produce a smaller molecule with optimised activity. Such an optimised peptide or protein fragment can then be protected *per se* in a second generation of patents, even if the protein is already known.

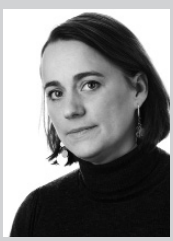
In line with G5/83, even if a protein or peptide is known *per se*, if its medical use has previously not been disclosed, patent protection may be obtained for the protein or peptide for any medical use. This is in contrast to the normal praxis of the EPO, where it is not possible to obtain protection for a product for a specific use. In addition, if a protein or peptide has been disclosed for a medical use, but for the treatment of a different pathological condition, it may still be possible to obtain protection for the protein or peptide in treating the newly identified pathological condition, that is a different technical effect of the protein or peptide. In addition, it is possible to protect pharmaceutical compositions comprising the protein or peptide, and even antibodies specific to the protein or peptide.

In contrast to peptides, most proteins are large molecules with a delicate, unique and complicated three-dimensional structure. The preparation, isolation and storage of such molecules, while retaining their biological activities, are therefore associated with numerous problems. Also, typically, natural sources for protein pharmaceuticals can lead to immune reactions and may contain viral and pathogen contaminations. Contrary to the smaller peptide drugs, which often can be synthesised using solid phase chemistry, most protein pharmaceuticals today are produced recombinantly. Thus, the method of production often constitutes important subject-matter for patent protection, as well as vectors containing the nucleotide sequence encoding the protein or peptide of interest. Again, due to the rapid development in modern biotechnology a skilled person is usually considered to be able to clone and express a gene in a fairly straightforward manner and according to T386/94 (for example), with a reasonable expectation of success.

The drafter's challenge

One of the challenges for the inventor in the field of protein pharmaceuticals is to draw up a patent application that is detailed enough to provide novelty, inventive step and sufficiency of disclosure while still providing a reasonable protection corresponding to the *de facto* contribution to the art.

Ylva Skoglösa



Ylva is a European patent attorney. She has a PhD in Medical Research and expertise within the areas of medical biotechnology, genetics, proteins and substances and devices for medical or dental treatment.

Ylva regularly assists potential investors and founding partners in evaluating third parties' IP positions, conducting freedom-to-operate and due diligence analyses. Prior to entering the IP profession, she did research work at the San Diego State University in California, the Max Planck Institute in Munich and the BMC in Uppsala. Before joining Valea in 2002 she worked for three years as a patent attorney at Plougmann & Vingtoft in Denmark. Ylva has been working in the IP field since 1999.

Annika Unge

Annika is a European patent attorney. She has a PhD in Biochemistry and specialises in patenting in the fields of medicine, biochemistry, microbiology, molecular biology and gene technology. She works with all patent issues including pre-patenting investigations, patent drafting and prosecution. Annika also works with business-related IP issues such as patent strategies, questions regarding validity, infringement, due diligence and freedom-to-operate issues.

Annika started working in the IP field in 2001. Before joining Valea in October 2003, she worked as a patent attorney at another Swedish IP law firm. Annika also has experience as a lecturer, both for internal training courses and external courses.

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