# The requirement of industrial applicability for pharmaceutical and biotechnological inventions

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# 1 Introduction

## 1.1 Overview

The main topic of this paper is the requirement of industrial application for pharmaceutical and biotechnological inventions, with a particular focus on how the requirement is being interpreted by the technical Board of Appeal of the European Patent Office.

According to Article 52 of the European Patent Convention, for an invention to be patentable within the European patent system, there are three main criteria that must be fulfilled. First of all, the invention must be "new", i.e. it cannot have been known at the time of invention. Secondly, it needs to involve an "inventive step". This requirement is commonly understood to mean that the steps taken to create the invention, cannot have been obvious to a person skilled in the art, based on the common knowledge in the field.

The final of the main criteria is that the invention must be "susceptible of industrial application". This is defined in Article 57 EPC as being able to "be made or used in any kind of industry, including agriculture."

In general, the lack of industrial applicability is rarely used as a reason to oppose or reject a patent.[1] This is partly caused by the fact that, traditionally, the threshold for meeting the requirement has been considered as rather low, since potential applications for an invention are generally fairly obvious.[2] Thus, the requirement of industrial applicability has not been regularly assessed by the Board of Appeal.

In the past few decades, however, patent applications filed for inventions in the biotechnological and pharmaceutical field have become more frequent, as techniques in the

[1] See Hector MacQueen et.al., *Contemporary Intellectual Property: Law and Policy*, 2nd edition, Oxford 2011 pp. 472-473.

[2] See Robert Fitt and Edward Nodder, "Setting the threshold for industrial application: the UK diverges from Europe", *Journal of Intellectual Property Law & Practice*, 2010, pp. 560-565 (p. 560). See also Bengt Domeij, *Pharmaceutical Patents in Europe*, Stockholm 2000 pp. 20-22.

field have advanced[3]. For inventions in this area, the industrial application is not always obvious, and newly discovered proteins expressed by isolated genes, or novel chemical compounds that participate in biological processes, might not have a definitively proven function when a patent application is filed.

Especially for inventions sought to be used in disease treatment, months or years of *in vitro*[4] and *in vivo*[5] trials may be necessary to conclusively determine how the substances actually function in the complex biological systems they are assumed to act. Parameters like efficacy or side effects, might not be determined until the very final stages of the development process.

As a result of this, patent applications are routinely filed before the invention has been definitely proven to function as desired. It is therefore of great importance for those developing new therapeutic agents, to know how the legislation should be understood.

For the most part, it will be fairly apparent whether or not an invention satisfies the requirements of novelty and inventive step. For these requirements, biotechnological and pharmaceutical inventions are in any case not vastly different from those in other fields. The correct understanding of the requirement of industrial application is therefore particularly important, as it effectively dictates how early in the development process a patent can be granted.

[3] According to the EPO, biotechnology patents have for the ”past several years” consistently ranked among the ten largest technical fields in terms of patents filed (see EPO’s website (epo.org), https://www.epo.org/news-issues/issues/biotechnology.html (last accessed 30 May 2016)).
[4] *In vitro*: ”biological processes and reactions occurring in (i) cells or tissues grown in culture or (ii) in cell extracts or synthetic mixtures of cell components” (Eleanor Lawrence (ed.), *Henderson’s Dictionary of Biological Terms*, 11th edition, Harlow 1995).
[5] *In vivo*: ”biological processes occurring in a living organism” (*Henderson’s Dictionary of Biological Terms*).

## 1.2 Questions to be examined in this paper

In defining a clear interpretation of the requirement in Article 57 EPC for industrial applicability, there are several questions that need to be answered. First of all, how the terms “industry” and “made or used in industry” should be understood must be determined. Specifically, the question here is whether reproducibility is adequate, or if something more substantial is required.

Secondly, it is important to determine what degree of function is necessary to satisfy the requirement. Is it, for example, sufficient that the claimed substance can be used as a research tool, or is it necessary to disclose a biological function, e.g. as a therapeutic agent?

Furthermore, it is essential to determine what should be disclosed in the patent application to support the claimed industrial application. What should, for example, be expected in terms of proof? Is it necessary to provide experimental evidence conclusively proving the claimed functions, or is it sufficient that the purported ways of exploiting the invention are merely plausible? Are results from computer-assisted *in silico*[6] experiments adequate evidence to support an assumed function, or are wet biology[7] experiments compulsory? What degree of quality should be expected from the disclosed evidence, and how much, if any, weight can be placed on evidence handed in after the filing date?

## 1.3 Method

As the European patent system is based on the “first to file” principle, answering the questions outlined above is important in order to determine at what time the filing of a patent application would be prudent. The goal being to make sure that sufficient evidence is presented at the filing date, while an excessive amount of time is not spent collecting evidence that is not required.

[6] *In silico*: Simulations done using computer-assisted methods.
[7] Wet-biology experiments: A collective term used about *in vitro* and *in vivo* experiments.

The reason for focusing on the multilateral rule in Article 57 EPC rather than national legislation is simple: most patent systems on the national level in Europe are largely, if not completely, based on the EPC. The interpretation of this rule will therefore be applicable also in national patent systems.

According to Article 31 (1) of the Vienna Convention,[8] the interpretation of a treaty should be done "in accordance with the ordinary meaning to be given to the terms of the treaty in their context and in the light of its objective and purpose." While the Vienna Convention has not been ratified by all member states of the European Patent Organisation,[9] it has been established that this convention should be considered a codification of international customary law[10], and it is thus a basis for interpreting conventions such as the EPC.

The literal understanding should thus be the foundation for an interpretation of the requirements that follow from the EPC. It is, however, not given that the interpretation should be solely based on the literal understanding of the terms. Particularly for conventions whose purpose is harmonisation of national legal systems, the practice of the convention will often be more important.[11] Where the practice comes from executive organs tasked with interpreting the convention, as is the case for EPO's Board of Appeal, their understanding of the terms should be given significant weight.

Additionally, there could be circumstances dictating that less importance should be placed the literal understanding of the terms of the convention. This is arguably the case for Article 57 EPC when assessed in relation to inventions in the pharmaceutical and biotechnological field.

[8] Vienna Convention on the law of treaties, 23 May 1969.
[9] "The European Patent Organisation is an intergovernmental organisation that was set up on 7 October 1977 on the basis of the European Patent Convention (EPC)". Cf. EPO's website (epo.org), https://www.epo.org/about-us/organisation.html (last accessed 31 May 2016).
[10] Morten Ruud and Geir Ulfstein, *Innføring i Folkerett*, 4th edition, Oslo 2011 p. 81.
[11] See Finn Arnesen and Are Stenvik, *Internasjonalisering og juridisk metode: særlig om EØS-rettens betydning I norsk rett*, 2nd edition, Oslo 2015 pp. 31-32.

Industrial application is defined only in broad strokes, and includes making or using the invention in all fields of industry.[12] As inventions in the field of pharmaceuticals and biotechnology by nature are quite different from inventions in most other technical fields,[13] a literal understanding of the requirement may not be the most advantageous.

> While the practice of the Board of Appeal is not actually binding to the member states, nor in other cases before the Board themselves, failure to conform with the standards formed here, could be detrimental to the harmonisation of the European patent system. Because European patents are granted by the EPO, but enforced by national courts, predictability is crucial. If different interpretations of the legislation are assumed in the different states, it could be difficult for applicants to determine if a patent granted by the EPO in fact will offer protection in the desired member states.
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> The consideration of legal unity therefore dictates that practice in the EPO should be attributed considerable weight, even when interpreting national law.[14] This, held together with the fact that there are not many examples of relevant practice on the national level, clearly indicates that it will be most sensible to base an analysis of the requirement of industrial applicability on the EPO's Board of Appeal and their interpretation of Article 57 EPC.

Consequently, determining how the rules in the EPC are practiced by the Board of Appeal, will be of the utmost importance when defining the effect of the requirements.

[12] Phillip W. Grubb, *Patents for Chemicals, Pharmaceuticals and Biotechnology*, 4th edition, Oxford 2004 p. 65.
[13] More on this in chapter 2.2 below.
[14] This has been confirmed by several national courts. See e.g. ruling by the Norwegian Høyesterett (Supreme Court) in Rt. 2008 s. 1555 (*Biomar*) paragraph (51) and ruling by English Court of Appeal in [2010] EWCA Civ 33 (*Eli Lilly and Company v Human Genome Sciences, Inc.)*

# 2 Background

## 2.1 The legal framework

Apart from several international agreements on patent law, like TRIPS[15] and PCT,[16] European patent law is coloured by rules issued from three different legal spheres.[17] First of all, the European Patent Office (EPO) grants patents according to the European Patent Convention (EPC),[18] a multilateral treaty with 38 member states, initiated by the European Council. Patents granted by the EPO are, however, not automatically valid in all member states. It is up to the applicant to define in the application the states in which he wants protection. National patents are then granted and enforced in the specified countries provided that the EPO approves the application.

The second legal sphere is made up of the national patent systems, as there are in fact slight variations between the different countries in legislation.

Lastly, the European Union constructs supranational legislation, attempting to form a continuous harmonisation of the member states' national patent laws. An example of this, is the so-called Biotech Directive,[19] which obviously is relevant for inventions in the pharmaceutical and biotechnological field.

[15] Agreement on Trade-Related Aspects of Intellectual Property Rights, Annex 1C of the Marrakesh Agreement Establishing the World Trade Organization (15 April 1994) – an international agreement setting minimum standards for intellectual property regulation.
[16] The Patent Cooperation Treaty (24 January 1970) – a multilateral patent law treaty, allowing applicants to seek patent protection in 148 member countries simultaneously.
[17] More in Timo Minssen, "När anses en bioteknologisk uppfinning vara komplett och praktiskt användbar? – Del II – Om senare utveckling kring kravet på "industrial application" och "utility" för gen- och protein-relaterade uppfinningar i USA och Europa", *Nordiskt Immateriellt Rettsskydd*, 2008, pp. 339-387 (pp. 340-341).
[18] The European Patent Convention, 15 October 1973. Currently, the 15th edition is in effect.
[19] Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions, 6 July 1998.

Additionally, in the past years, efforts have been made to implement a common, multilateral patent (as opposed to one organ granting patents for specified countries).[20] This has resulted in the Unified Patent Court,[21] which will have "exclusive jurisdiction for litigation relating to European patents and European patents with unitary effect",[22] and will enter into force as soon as it has been ratified by the required number of states.

Because there are several different patent systems currently in effect in Europe, there is also a large potential for conflict. One of the most actively debated subjects, is regarding the correct interpretation of the requirement for industrial applicability, particularly in assessment of patent applications for gene and protein related inventions.[23]

### 2.1.1 The Biotech Directive

The Biotech Directive has had a central role in the discussion of how the requirement of industrial applicability should be interpreted. While the Directive does allow for patents to be granted for isolated gene sequences, Article 5 (3) prescribes that "[t]he industrial application of a sequence or a partial sequence of a gene must be disclosed in the patent application."

It follows from the Biotech Directive that gene related inventions should be considered on the basis of the same criteria as all other inventions. It does, however, also imply that the industrial application of a whole or partial gene sequence will never be considered as obvious. A DNA sequence must have a disclosed function, and If the gene sequence is shown to encode a protein, the function of the encoded protein must also be provided. If several gene sequences are claimed in the application, the functions of all sequences must be disclosed.

[20] See COM(2007) 165 - Communication from the Commission to the European Parliament and the Council – Enhancing the patent system in Europe, 3 April 2007.
[21] The Unified Patent Court is established in the Agreement on a Unified Patent Court and Statute, document 16351/12 of 11 January 2013.
[22] See EPO's website (epo.org) https://www.epo.org/law-practice/unitary/patent-court.html (Last accessed 28 May 2016).
[23] See Minssen, 2008 p. 341.

While the Biotech Directive undoubtedly is important in the clarification of legal protection for biotechnological inventions, it is not absolutely imperative in the elucidation of how the requirement of industrial application is interpreted by the EPO. According to Rule 26 (1) EPC, the Directive "shall be used as a supplementary means of interpretation", but in reality, it is rarely mentioned by the Board of Appeal.

### 2.1.2 The European Patent Convention

Industrial applicability is one of the fundamental requirements in European patent law, and is first and foremost anchored in Article 52 (1) EPC, which states that "European patents shall be granted for all inventions, in all fields of technology, provided that they are new, involve an inventive step and are susceptible of **industrial application**" (emphasis by author).

From Article 57 EPC, it follows that an invention will be considered "as susceptible of industrial application if it can be made or used in any kind of industry, including agriculture", and Rule 42 (1) (f) EPC states that the description of the patent application must "indicate explicitly, unless it is obvious from the description or the nature of the invention, the way in which the invention may be exploited in industry."

For complete and partial gene sequences, further specification is found in Rule 29 (3) EPC, a literal inclusion of Article 5 (3) of the Biotech Directive: "[t]he industrial application of a sequence or a partial sequence of a gene must be disclosed in the patent application". Hence, it follows from this that the industrial application of DNA sequences will not be considered as "obvious".

The technical Board of Appeal has, for several gene- and protein-related inventions, acknowledged industrial applicability according to Article 57 EPC, especially for inventions that have proved to have valuable pharmaceutical capabilities directly applicable to animal trials within the pharmaceutical industry. For the most part, however, the specific industrial

applications have been so plausible and clearly stated in the patent applications, that the Board neither discussed nor mentioned Rules 29 (3) or 42 (1) (f) EPC.[24]

Most of the decisions have not, therefore, given satisfying answers to the question asked above. However, more complex cases have been put forward for the Board of Appeal, and there are consequently several examples of a more thorough examination of the requirement of industrial applicability.

## 2.2 Biotechnological and pharmaceutical inventions

Since before morphine was extracted from the opium plant and marketed for pain management in the early 1800s, the pharmaceutical industry has played a key role in the continued advancement of human health. Were it not for the prospects of financial gain, it is highly unlikely that the treatment of disease would be near the level at which it is today.

The pharmaceutical industry has a collective yearly revenue exceeding $1000 billion.[25] Consequently, there are undoubtedly many asking questions regarding the ethical aspects of pharmaceutical patents, arguing that therapeutic agents should be available to all, and that no one should be profiting from human disease.[26]

There are, however, also enormous costs associated with the development of new drugs. Large teams of scientists are generally needed, and prospective therapeutic agents must go through extensive testing before they are allowed on the market.

After identifying the lead compound, i.e. the compound performing the final function in a biological system, work starts on improving the potency, reducing toxicity and refining

[24] See e.g. T 446/99 (*Bordetella toxin/AMGEN*), T 606/03 (*Gene trap/ARTEMIS*), T 1074/03 (*Soluble peptides/IXSYS*)
[25] See Thomson Reuters website (thomsonreuters.com), http://thomsonreuters.com/en/articles/2015/global-pharma-sales-reach-above-1-trillion.html (last accessed 31 May 2016).
[26] See e.g. Sigrid Sterckx, ”Can drug patents be morally justified?” *Science and Engineering Ethics*, **11** (1), 2005 pp. 81-92.

binding specificity, as well as improving the duration of action and metabolic and pharmacokinetic patterns.[27] According to a study done by the Tufts Center for the Study of Drug Development, the average cost of developing a drug gaining market approval, was $2.6 billion. This study also found that an additional §312 million is spent on further testing after approval of the drug, bringing the total to §2.9 billion.[28]

Consequently, there is great importance placed on having intellectual protection and securing the investments made in research and development.[29] This has resulted in patents being sought at every step from inception to market place, which could lead to "dense thickets of intersecting, overlapping, and cross-blocking patents",[30] as everyone involved is trying to gain control of the final product.

A possible consequence of this has been described as the "tragedy of the anticommons". A situation in which resources are prone to underuse because many different owners have a right to exclude others from a limited resource. If, for example, all receptors[31] that could be used in screening tests were controlled by different owners, collecting the necessary licences to screen potential drugs against these receptors would be near impossible. As a result, scientific progress could decelerate, as less promising alternatives would be pursued if they were to present fewer hurdles.[32]

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[27] See George de Stevens, "Lead Structure Discovery and Development" in Corwin Hansch (ed.) *Comprehensive Medicinal Chemistry*, Oxford 1990, pp. 261-284 (p. 266).
[28] Joseph A. DiMasi, Henry G. Gabrowski and Ronald W. Hansen, "Innovation in the pharmaceutical industry: New estimates of R&D costs", *Journal of Health Economics*, 2016 pp. 20-33 (p. 20).
[29] More in Philippe Ducor, "New Drug Discovery Technologies and Patents", *Rutgers Computers & Technology Law Journal*, 1996 pp. 369-477 (p. 461).
[30] See Thomas D. Kiley, "Patents on Random Complementary DNA Fragments?" *Science*, **257** (5072), pp. 915-918 (p 916). Also Domeij, 2000, pp. 19-38.
[31] Receptor (here): protein to which a signalling molecule such as a neurotransmitter, hormone, drug, or metabolite binds specifically and stimulates a particular response by the cell (*Henderson's Dictionary of Biological Terms*).
[32] More in Michael A. Heller and Rebecca S. Eisenberg, "Can Patents Deter Innovation? The Anticommons in Biomedical Research", *Science*, 1998 pp. 698-701 (p. 699)

The practice of filing patent applications before a function has been definitively proven is especially evident in the field of biotechnology.[33] In short, biotechnology is the use of living organisms to create useful products, for example pharmaceuticals. In the 1970s, scientists were beginning to find techniques for locating, isolating, preparing and studying small segments of DNA. As the techniques for cloning DNA improved, the field of proteomics[34] emerged, enabling the study of all genes and proteins in whole cells.

All functions occurring in a biological system are essentially carried out by proteins. These proteins are expressed from the genetic information stored in the DNA. Using different biotechnological methods, scientists are able to identify and isolate genes and proteins. As the areas of genomics[35] and proteomics have evolved, large libraries of genes and proteins isolated from different organisms (including humans) have been created. This allows for comparison of newly discovered substances, with substances that have known functions, normally by carrying out some sort of sequence homology assay.

In the pharmaceutical area, biotechnology is first of all used to identify receptors or enzymes[36] involved in a specific process related to a disease, and then finding a substance that can interfere with its action.

Furthermore, several diseases are effectively treated with recombinant proteins produced using biotechnological methods. A few examples are: Erythropoietin[37] which can help people

[33] For a far more thorough description of the uses and methods of biotechnology, see See David L. Nelson and Michael M. Cox, *Lehninger Principles of Biochemistry*, New York 2013, pp. 435-436.
[34] Proteomics: ”Broadly, the study of the protein complement of a cell or organism” (glossary in Nelson and Cox, 2013).
[35] Genomics: ”A science devoted broadly to the understanding of cellular and organism genomes” (glossary in Nelson and Cox, 2013).
[36] Enzyme: ”any of a large and diverse group of (mainly) proteins that function as biological catalysts in virtually all biochemical reactions, essential in all cells, different enzymes being highly specific for a particular chemical reaction and reactants” (*Henderson’s Dictionary of Biological Terms*).
[37] Erythropoietin: ”a glycoprotein hormone produced chiefly by the kidney and which stimulates the final differentiation of red blood cells from precursor cells” (*Henderson’s Dictionary of Biological Terms*).

with reduced kidney function avoid frequent blood transfusions; insulin,[38] which is used in the treatment of diabetes; and interleukins,[39] used in the treatment of HIV infections, cancer and various immune deficiencies.

As the use of biotechnology and recombinant proteins[40] is becoming more and more common in therapeutics, the practice of attempting to gain patent protection at the earliest stages of research and development is also increasingly typical. Patent applications are routinely filed for partial gene sequences, which cannot be used to express full and functioning proteins.[41] Because elucidating the biological function of the full gene and the protein it encodes is the most expensive step in the process, embarking on that task becomes even more unattractive if several fragments of the full gene are already patented.[42]

While the potential use for most inventions is fairly obvious, this is, as follows from the above, often not the case for inventions in the field of pharmaceuticals and biotechnology. Whereas all identified and isolated proteins or chemical compounds can technically be reproduced (or "made"), the endogenous functions of such substances are often referred to indistinctly, and based on similarity with substances whose functions are better elucidated, as extensive research is required for these to be uncovered.[43]

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[38] Insulin: "a polypeptide hormone produced … in the pancreas, which decreases the amount of glucose in the blood by promoting glucose uptake by cells and increasing the capacity of the liver to synthesize glycogen" (*Henderson's Dictionary of Biological Terms*).

[39] Interleukins: "diverse group of proteins produced by activated macrophages and lymphocytes and other leukocytes during an immune response" (*Henderson's Dictionary of Biological Terms*).

[40] Recombinant protein: "any protein protein produced from a recombinant DNA template." Recombinant DNA: "DNA produced by joining together *in vitro* genes from different sources or which has in some way been modified *in vitro* to introduce novel genetic information" (*Henderson's Dictionary of Biological Terms*).

[41] A partial gene sequence can, in reality, only function as a probe to scan for the full gene. It cannot be used to encode a full, functioning protein, and thus will not cause any biological function. Partial gene sequences can, however be useful in diagnosis of genetic diseases.

[42] See Domeij, 2000 p. 27.

[43] More in Denis Schertenlieb, "The Patentability and Protection of DNA-based Inventions in the EPO and the European Union", *European Intellectual Property Review*, 2003 pp. 125-138 (p. 128).

As a result of this, clearly defining the correct interpretation of the requirement of industrial applicability is particularly important, as it may help to limit the ability to grant patents that in reality only function as means of hindering competitors from using particular substances in their research. A clear understanding of the requirement will also aid in determining when a patent application should be filed.

## 2.3 The line between discovery and invention

Discoveries are, according to Article 52 (2) (a) EPC, excluded from patentability, as they "shall not be regarded as inventions".

Since the potential use of inventions historically has been quite evident, there generally has been no real need for a separate evaluation of industrial applicability. Rather than explicitly evaluating the requirement of industrial applicability, the question has therefore largely been whether the claimed product is aimed at a technical result, or whether it is merely of an abstract and intellectual character,[44] and thus falling under the exclusions listed in Article 52 (2) EPC. The nature of biotechnological and pharmaceutical inventions, however, can often cause the distinction between invention and nonpatentable discoveries to become blurred.[45]

The line between discovery and invention has been discussed by the EPO Board of Appeal on several occasions. Discoveries has been defined as "the result of purely intellectual activity with no practical or or technical character", and it has been stated that the question of whether the claimed substance is a "mere "discovery"" is closely linked to the question of whether the way in which a claimed product could be "exploited in industry", may be derived from the description, or if the described product is "merely an interesting research result that might yield a yet to be identified industrial application".[46]

[44] See e.g. T 22/85 (*Document abstracting and retrieving/IBM*), point 2 of the reasons.
[45] See Schertenlieb, 2003 p. 127.
[46] T 338/00 (*Multimeric receptors/SALK INSTITUTE*), point 2 of the reasons.

This seems to mean that a substance should be considered as a discovery if no industrial application can be derived from the description in the patent application. This understanding is also assumed in literature. According to Minssen, for example, the Board of Appeal has implied that industrial applicability should be considered as an integral part of the term "invention".[47]

To be considered an invention and not merely a discovery, a claimed product must therefore have a clear practical application in a field of industry. The definition of the requirement in Article 57 EPC is consequently incredibly important.

# 3 The requirement of industrial application

## 3.1 "Industry"

Article 57 EPC reads as follows: "[a]n invention shall be considered as susceptible of industrial application if it can be made or used in any kind of industry, including agriculture." In the evaluation of the requirement of industrial application, the term "industry" is therefore obviously central.

There is, however, no definition of the term "industry" in the EPC or in the Biotech Directive. Consequently, it is necessary to look at the case law in order to determine how it should be interpreted.

It seems quite clear from practice in the EPO's Board of Appeal, that the term "industry" should be interpreted in a wide sense. This follows from several decisions, but is most often attributed to T 870/04 (*BDP1 phosphatase/MAX PLANCK*).

In this case, the claimed substance was a protein called brain derived phosphatase 1 (or BDP1). The application suggested that the claimed protein might be a part of the tyrosine

[47] See Minssen, 2008 p. 354.

phosphatase family,[48] and that it therefore would be involved in cellular mechanisms, such as down-regulating cell proliferation,[49] which would indicate a function in cancer treatment.[50]

Examining the industrial applicability of the invention, the Board states that "the notion of "industry" has to be interpreted broadly to include all manufacturing, extracting and processing activities that are carried out continuously, independently and for financial (commercial) gains".[51]

In addition to being confirmed in several decisions by the Board of Appeal,[52] the wide interpretation of "industry" has also been assumed in literature. It is, for example, listed by Minssen as the first of six principles derived from practice in the EPO.[53] Additionally, the interpretation has been adopted by national courts , as in the case of Eli Lily Co. vs. Human Genome Sciences. Here, Lord Justice Jacob lists the broad understanding of "industry" as one of ten guidelines for assessing the industrial application of biotechnology inventions.[54]

[48] Phosphatases are enzymes that may function as modulators of cellular processes by removing a phosphate group from the substrate binding to it. In general, dephosphorylation by a phosphatase will turn a cellular funcion off, while phosphorylation by the corresponding kinase will turn the function on. Tyrosine phosphatases in particular, have been shown to be involved in controlling signalling pathwyas in a number of fundamental physiological processes (see Qing Yang et al., "Cloning and Expression of PTP-PEST a novel, human, nontransmembrane protein tyrosine phosphatase", *The Journal of Biological Chemistry*, 1993 pp. 6622-6628 (p. 6622), referred to in the decision as "Document D1". See also Nicholas K. Tonks, "Protein tyrosine phosphatases: from genes, to function, to disease", *Nature Reviews Molecular Cell Biology*, 2006 pp. 833-846 (p. 833).
[49] Cell proliferation: "increase [in cell number] by cell division" (*Henderson's Dictionary of Biological Terms*).
[50] T 870/04 (*BDP1 phosphatase/MAX PLANCK*), point 8 of the reasons. See also the appellant's argument, point IX.
[51] *Op.cit*., point 2 of the reasons. The Board also refers to previous decision T 144/83 OJ EPO, 301, point 5 of the reasons.
[52] See e.g. T 641/05 (*GPCR-like receptor/PHARMACIA*), point 2 of the reasons.
[53] Minssen, 2008 p. 375.
[54] [2010] EWCA Civ 33, Eli Lily and Company v Human Genome Sciences, Inc. See also Fitt and Nodder, 2010, Box 1 on p. 564.

## 3.2 "Made or used in industry"

Article 57 EPC states that an invention will be "considered as susceptible of industrial application if it can be **made or used in any kind of industry**, including agriculture" (emphasis by author). The most obvious understanding of this, is that so long as the invention can be reproduced ("made"), by means of an industrial process, it will be susceptible of industrial application. This may not, however, be the most fortunate way of interpreting the term, as it might lead to a system in which patents are effectively used as "hunting licences", reserving entire fields of research for the patentees.[55]

The next question that needs to be examined, therefore, is how the term "can be made or used in … industry" in Article 57 EPC should be understood. This is a question that has been assessed several times by the EPO, and the answer does seem to be well established.

In *ICOS/V28 seven transmembrane receptor*, one of few cases concerning the requirement of industrial applicability that have been assessed by the EPO's opposition division, a patent had been opposed (among other reasons) because it allegedly did not fulfil the requirement of Article 57 EPC.

The patent covered a gene sequence and the protein it encoded, V28 seven transmembrane (V28 7TM) receptor. In the specification, it was predicted that the V28 protein structure would comprise seven hydrophobic domains separated by hydrophilic domains and residues which are conserved within a group of proteins called seven transmembrane (7TM) receptors.[56]

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[55] Minssen, 2008 p. 381.

[56] Seven transmembrane receptors, or G-protein coupled receptors (GPCRs) constitute the largest, most ubiquitous and most versatile family of membrane receptors and are the most common target of therapeutic drugs. The receptors are located in the cell membrane and are, as the name suggests, characterized by having seven distinct membrane spanning domains and coupled with guanine nucleotide-binding proteins (G-proteins). When a ligand binds to the receptor, it causes a conformational change in the molecule and the G-protein is activated, making it a molecular "switch". See e.g. Nina Wettschureck and Stefan Offermanns, "Mammalian G Proteins and Their Cell Type Specific Functions", *Physiological Reviews*, 2005 pp. 1159-1204 (pp. 1160, 1163).

The specification also stated that host cells expressing products of the V28 7TM gene would be useful in the large scale production of V28 7TM protein, and that antibodies[57] reacting with V28 7TM protein would be useful in complexes for immunisation to generate anti-idiotypic antibodies,[58] purifying V28 peptides and for identifying cells producing V28 protein.

It was suggested that ligands[59] (antibodies, agonists[60] and antagonists[61]) of V28 protein could be useful in modulating binding reactions involved in immunological and/or inflammatory processes *in vivo.* No antibodies, agonists or antagonists were, however, disclosed in the application, and any involvement of the protein in such processes was not demonstrated.[62]

The patentee argued that because the application disclosed how to make, and proposed functions for, the claimed V28 protein, the requirement for industrial application must be satisfied.

The opposition division did not agree, and stated that the requirement would not be fulfilled just because "the specification shows that V28 can be made and can be used."[63] Thus it seems that the term "made or used … in industry" should not be understood literally, an interpretation which is also adopted in several decisions by the technical Board of Appeal.

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[57] Antibody: a serum protein which is formed in response to an antigenic stimulus and reacts specifically with that antigen; antigen: a substance which elicits the synthesis of an antibody with which it specifically reacts (Emery's Elements of Medical Genetics).
[58] An anti-idiotypic antibody can bind to other antibody molecules, inhibiting their binding to their respective antigens (more in Ying Pan, Stacieann C. Yuhasz and L. Mario Amzel, "Anti-idiotypic antibodies: biological function and structural studies", *Federation of American Societies for Experimental Biology Journal*, 1995 pp. 43-49 (p. 43).
[59] Ligand: "any molecule that binds specifically to another molecule. Examples are a hormone binding to its receptor, an inhibitor binding to an enzyme, oxygen binding to haemoglobin, and antigen binding to an antibody" (*Henderson's Dictionary of Biological Terms).*
[60] Agonist (here): "substance responsible for triggering a response in a cell, such as a hormone, neurotransmitter, etc." (*Henderson's Dictionary of Biological Terms*).
[61] Antagonist (here): "any substance that counteracts the effect of a hormone, neurotransmitter, drug, etc." (*Henderson's Dictionary of Biological Terms*).
[62] OJ EPO 2002, 6 (*ICOS/V28 seven transmembrane receptor*), point 9 (i).
[63] *op.cit.*, point 9.

In T 870/04 (*BDP1 phosphatase/MAX PLANCK*),[64] the application did not, according to the Board, disclose sufficient evidence to make the proposed functions plausible. While there was little doubt of the involvement of tyrosine phosphatases in down-regulating their corresponding kinases and their catalytic activity in cell proliferation, the suggested functions of the claimed protein were largely based on the known functions of similar proteins.

Eventually, it was concluded that the only probable function disclosed, was the ability to produce the protein itself. It was stated that:

> "The requirement of Article 57 EPC that **the invention** "can be made or used" in at least one field of industrial activity emphasizes that a "practical" application of the invention has to be disclosed. Merely because a substance (here: a polypeptide) could be produced in some ways does not necessarily mean that this requirement is fulfilled, unless there is also some profitable use for which the substance can be employed" (emphasis by the Board).[65]

This then confirms the interpretation in *ICOS/seven transmembrane receptor*, that something more substantial is required from the invention than it simply being able to be made and used.

In the assessment of industrial applicability in T 898/05 (*Hematopoietic receptor/ZYMOGENETICS*), the Board states that even if the structure of a product is given, and it therefore can be reproduced, a patent cannot be granted if the function is "undetermined or obscure or only vaguely indicated".[66] If patents were granted in such situations, the patentee would gain "unjustified control over others who are actively investigating in that area and who might eventually find actual ways to exploit it".[67]

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[64] See above in chapter 3.1.
[65] T 870/04 (*BDP1 phosphatase/MAX PLANCK*), point 4 of the reasons.
[66] T 898/05 (*Hematopoietic receptor/ZYMOGENETICS*), point 7 of the reasons.
[67] *Ibid*.

Further specification of the term can be found in T 338/00 (*Multimeric receptors/SALK INSTITUTE*). Here, the patent application covered a receptor reportedly belonging to the steroid/thyroid hormone receptor superfamily,[68] purported to form heterodimeric receptors[69] with other members of the superfamily. These heterodimeric receptors would in turn function as modulators of "suitable expression systems".[70]

The core of the discussion regarding the industrial application is whether the way in which the invention may be exploited in industry, may be derived from the description, or if it what presented is "merely an interesting research result that might yield a yet to be identified industrial application".[71] The Board did find that the applicant had provided ample evidence of not only the cooperative interactions forming the heterodimeric receptors, but also of the use of these receptors for "modulating suitable transcription expression systems", and their relevance in several biological processes.[72]

It is stated that "[t]he activities and product disclosed in the application are not aimed at an abstract or intellectual character but at a direct technical result that may clearly be applied in an industrial activity".[73]

Thus, it follows from this decision that in order for an invention to be susceptible of industrial application, it must have a concrete, technical use that can be employed in a field of industry. If the proposed functions are too broad and abstract, industrial applicability cannot be acknowledged.

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[68] The steroid/thyroid hormone receptor superfamily is a family of proteins binding to steroid or thyroid hormones. Such receptor proteins have great therapeutic implications, as they could be used in treatment of a variety of hormone related diseases (see Pengxiang Huang, Vikas Chandra and Fraydoon Rastinejad, "*Structural* Overview of the Nuclear Receptor Superfamily: Insights into Physiology and Therapeutics", *Annual Review of Physiology*, 2010 pp. 247-272).

[69] Heterodimeric receptors: a receptor composed of two different protein subunits (see Henderson's Dictionary of Biological Terms).

[70] T 338/00 (*Multimeric receptors/SALK INSTITUTE*), point 3 of the reasons.

[71] *Op.cit.*, point 2 of the reasons.

[72] T 338/00 (*Multimeric receptors/SALK INSTITUTE*), point 3 of the reasons.

[73] Ibid.

## 3.3 "Function"

It has been established that the patent application must disclose a practical way to exploit the invention. The core of the assessment of the requirement in Article 57 EPC, particularly as it pertains to inventions in the field of pharmaceuticals and biotechnology, thus appears to be what *function* the claimed substance performs. Consequently, it must also be determined what should be expected from the disclosed function.

As mentioned above, it follows from T 338/00 (*Multimeric receptors/SALK INSTITUTE*) that the invention must have a concrete, technical result that may clearly be applied in an industrial activity.[74]

This is further specified in T 870/04 (*BDP1 phosphatase/MAX PLANCK*), where the Board states:

> "although the present application described a product (a polypeptide), means and methods for making it, and its prospective use thereof for basic science activities, it identifies no practical way of exploiting it in at least one field of industrial activity. In this respect, it is considered that a vague and speculative indication of possible objectives that might or might not be achievable by carrying out further research with the tool as described is not sufficient for fulfilment of the requirement of industrial applicability. The purpose of granting a patent is not to reserve an unexplored field of research for an applicant."[75]

The Board concedes that there is no doubt that the protein would be usable as a research tool in the further investigation of the role phosphatases and kinases play in cellular signalling systems, and perhaps also for diagnostic or therapeutic purposes. The application does, however, leave it to the skilled reader to uncover these functions by carrying out extensive research programmes.

[74] T 338/00 (*Multimeric receptors/SALK INSTITUTE*), point 3 of the reasons.
[75] T 870/04 (*BDP1 phosphatase/MAX PLANCK*), point 21 of the reasons.

Moreover, the Board emphasises that the application must disclose "some profitable use for which the substance can be employed".[76] This goes a long way to define what is required of the function, as the use of the invention must be translatable to commercial gain.

Consequently, it will often not be adequate that the invention can be used as a research tool. Rather, it must have concrete function that can be employed for e.g. therapeutic or diagnostic purposes. That the invention can be used to carry out research on itself is not sufficient to satisfy the requirement.

Thus, the conclusion in T 870/04 (*BDP1 phosphatase/MAX PLANCK*), is that even though the application disclosed a protein, how to isolate and reproduce this protein and prospective uses in research activities, "it identifies no practical way of exploiting it in at least one field of industrial activity".[77] Because it was not at all certain that the objectives given in the application would be achievable by using the invention as a research tool, the requirement of industrial application was not satisfied.[78] It is also stated that:

> "In cases where a substance, naturally occurring in the human body, is identified, and possibly also structurally characterised and made available through some method, but either its function is not known or it is complex and incompletely understood, and no disease or condition has yet been identified as being attributable to an excess or deficiency of the substance, and no other practical use is suggested for the substance, then industrial applicability cannot be acknowledged."[79]

What can be derived from this decision, is that a function that can be directly put to "profitable use" must be disclosed in the application. If the disclosed functions are based on speculations, and further research is required to confirm an actual industrial application, the requirement of Article 57 EPC is not fulfilled.

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[76] T 870/04 (*BDP1 phosphatase/MAX PLANCK*), point 6 of the reasons.
[77] *Op.cit.*, point 21 of the reasons.
[78] See Rainer Moufang "Patentability of pharmaceutical innovations" in Josef Drexl and Nari Lee (eds.), *Pharmaceutical Innovation, Competition and Patent Law*, Cheltenham 2013 pp. 80-81.
[79] T 870/04 (*BDP1 phosphatase/MAX PLANCK*), point 6 of the reasons.

This interpretation is confirmed in T 898/05 (*Hematopoietic receptor/ZYMOGENETICS*), where the claimed invention is a DNA sequence encoding a protein called Zcytor1. The application describes Zcytor1 as a "cytokine[80] receptor with a role in proliferation, differentiation[81] and activation of immune cells". It was also suggested that the protein might play a role in the development and regulation of immune responses.

The Board makes it clear that a disclosed function is essential for determining industrial applicability of a newly discovered protein, because "the function is the gateway to understanding the concrete benefits which may derive from exploiting the invention industrially".[82]

Referring to T 870/04 (*BDP1 phosphatase/MAX PLANCK*) and the term "profitable use" as a threshold for adequate function, the Board states that rather than understanding "commercial gain" as a potential for economic profit, it should be "understood in the wider sense that the invention claimed must have such a sound and concrete technical basis that the skilled person can recognise that its contribution to the art could lead to practical exploitation in industry".[83] The expression "profitable use" could therefore be understood as "immediate, concrete benefit".[84]

The requirement is further clarified as the Board states that "a product which is definitely described and plausibly shown to be usable, e.g. to cure a rare or orphan disease, might be considered to have a profitable use of concrete benefit, irrespective of whether it is actually intended for the pursuit of any trade at all".[85] Products of such nature will there fore meet the requirement of industrial application.

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[80] Cytokine: "any protein factor such as a growth factor, which is a product of a cell and which affects the growth and division, or other functions, of other cells" (*Henderson's Dictionary of Biological Terms*).
[81] Cell differentiation: "the development of cells with specialized structure and function from unspecialized precursor cells" (*Henderson's Dictionary of Biological Terms*).
[82] T 898/05 (*Hematopoietic receptor/ZYMOGENETICS*), point 20 of the reasons.
[83] *Op.cit.*, point 5 of the reasons.
[84] *Op.cit.*, point 6 of the reasons.
[85] *Op.cit*., point 8 of the reasons.

It is clear from this, that "profitable use" should be interpreted as "beneficial use", so that it relates to a concrete benefit to society, rather than simply an economic benefit for the patentee.

For the invention in question, the Board found that although the details of the biochemical activity and cellular function were not disclosed in the application, the therapeutic treatments that could be derived directly from the functions suggested by results from computer-assisted experiments "cannot be considered to be so "vaguely defined" that they do not suggest any therapeutic or diagnostic use."[86] Furthermore, the Board found that the therapeutic functions proposed by the application were plausibly related to the disclosed structure of the protein.

The protein was therefore not just a simple research tool that could only be used to do further research in the quest for an industrial application.

It seems clear that the main point in the assessment of industrial applicability should be whether or not the technical contribution is useful to the point that society may reap from it an immediate benefit. If a naturally occurring substance known to have a function of major importance to human health is identified and isolated, this will immediately indicate a practical use and therefore also industrial applicability.

It does, however, follow from T 604/04 (*PF4A receptors/GENENTECH*), that a product does not need to be immediately or directly available for use in the treatment of diseases for it to be deemed as displaying an "immediate concrete benefit".

In this case, the application covered the identification of various DNA sequences encoding several polypeptides functioning as receptors for the PF4A superfamily of cytokines.

[86] T 898/05 (*Hematopoietic receptor/ZYMOGENETICS*), point 31 of the reasons.

It follows from this decision that "the skilled person" should be able to reproduce "without undue burden" the claimed invention, on the basis of what is disclosed in the patent specification.[87]

The Board does state that the "technical data" for some of the claimed polypeptides "fall somewhat short" of fulfilling the criteria defined in T 870/04 (*BDP1 phosphatase/MAX PLANCK*),[88] as no evidence was disclosed as to which ligands would bind to the claimed proteins. However, it is specified, that "the common general knowledge at the priority date" has to be taken into account.[89]

Looking to existing research therefore, the Board found clear evidence to support that the PF4A family of cytokines at the priority date were attractive agents for development of new pharmaceuticals, as research indicated that inhibition of their activity could improve wound healing and tissue repair.[90]

Hence, the Board concluded that the PF4A family of chemokines[91] at the priority date were "considered not only to be interesting in fundamental research but also as important for the pharmaceutical industry **irrespective** of whether or not their role had been clearly defined"[92] (emphasis by the Board). It was also clear from the prior art that the function of chemokines is determined through the receptors they bind to, and it was therefore concluded that the receptors had to be equally important. As a result, the requirement of industrial applicability had to be satisfied.[93]

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[87] T 604/04 (*PF4A receptors/GENENTECH*), point 22 of the reasons.
[88] Cf. T 870/04 (*BDP1 phosphatase/MAX PLANCK*), point 6
[89] T 604/04 (*PF4A receptors/GENENTECH*), point 15 of the reasons.
[90] *Op.cit.*, point 17 of the reasons, referencing Mark Y. Stoeckle and Kimberly A. Barker, "Two Burgeoning Families of Platelet Factor 4-Related Proteins: Mediators of the Inflammatory Response", *The New Biologist*, 1990 pp. 313-323.
[91] PF4A proteins are members of the cytokine subcategory chemokines, which are involved in inflammatory response. See Stoeckle and Barker, 1990 p. 313.
[92] T 604/04 (*PF4A receptors/GENENTECH*), point 18 of the reasons.
[93] *Ibid*.

Thus, it follows that if a substance is considered to be of great importance for the development of new therapeutic agents, it might be permissible not to have clearly defined its function at the time the patent application is filed.[94]

## 3.4 Disclosure

### 3.4.1 Proof of function

#### *3.4.1.1 Standard of proof*

In order to establish the earliest point at which an applicant can reasonably expect a patent to be granted, it is imperative to determine what evidence must be disclosed in the application

When determining the evidence that is required for industrial applicability to be acknowledged, it must first be decided what is the actual standard of proof. Is it sufficient that the proposed application is *plausible* when looking at the prior art and common general knowledge, or must the function be demonstrated through experiments?

The patent application in T 1329/04 (*Factor-9/JOHN HOPKINS*) covered the polypeptide growth differentiating factor-9 (GDF-9), and DNA sequences encoding proteins having GDF-9 activity. These proteins were assumed to be part of the transforming growth factor-β (TGF-β) family, a group of proteins that are involved in cell growth and differentiation, and thus have significant therapeutic implications.[95]

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[94] See Moufang, 2013 p. 81.

[95] Drugs affecting TGF-β signalling are used in treatment of e.g. **heart disease** (see Lim, H. and Zhu, Y. Z., "Role of transforming growth factor-beta in the progression of heart failure", *Cellular and Molecular Life Sciences,* 2006 pp. 2584-2596), **cancer** (see Gerard C. Blobe, William P. Schiermann and Harvey F. Lodish, "Role of Transforming Growth Factor β in Human Disease", *New England Journal of Medicine*, 2000 pp. 1350-1358 (pp. 1351-1354)), obesity. Davina Wu et al., "Eosinophils Sustain Adipose Alternatively Activated Macrophages Associated with Glucose Homeostasis", *Science*, 2011 pp. 243-247), and **Multiple Sclerosis** (see Ramesh K. Selvaraj and Terrence L. Geiger, "Mitigation of Experimental Allergic Encephalomyelitis by TGF-β Induced Foxp3$^{+}$Regulatory T Lymphocytes through the Induction of Anergy and Infectious Tolerance", *Journal of Immunology*, 2008 pp. 2830-2838). Recent research has also indicated that TGF-β signalling might be involved in **Alzheimer's disease**

It is stated in the decision that the question to be investigated is "whether or not it is **plausible** that the molecule … constitutes a further member of the TGF-β superfamily"[96] (emphasis by author). Furthermore, the Board also states that "[t]he definition of an invention as being a contribution to the art, i.e. as solving a technical problem and not merely putting forward one, requires that it is at least made plausible by the disclosure in the application that its teaching solves indeed the problem it purports to solve".[97]

*Plausibility* is also the threshold assumed in T 604/04 (*PF4A receptors/GENENTECH*). Here the Board, with regards to the claimed proteins, states that "[t]he first question which arises is whether or not these are bona fide solutions to the above defined problem".[98] Subsequently the decision in T 1329/04 (*Factor-9/JOHN HOPKINS*)[99] is cited, before the Board states that "there is no absolute certainty that the polypeptides of Figures 4 and 5 [the claimed proteins] are receptors for members of the PF4A family of cytokines – to which IL-8 belongs – yet, in the board's judgment, the above mentioned structural features make it plausible that this is indeed the case."[100]

That the structures of the disclosed proteins make it plausible that they are in fact receptors for PF4A cytokines, seems to be sufficient, as the Board continues onto answering the question of whether or not the claimed proteins may be considered "inventive".

Plausibility as the standard of proof is confirmed in T 898/05 (*Hematopoietic receptor/ZYMOGENETICS*), where industrial applicability was also acknowledged by the Board of Appeal. In this decision, it is stated that because no evidence from the prior art suggested that the proposed functions of the Zcytor1 protein would not be directly linked to

(see Walter Swardfager et al., "A Meta-Analysis of Cytokines in Alzheimer's Disease", *Biological Psychiatry*, 2010 pp. 930-941).

[96] T 1329/04 (*Factor-9/JOHN HOPKINS*), point 6 of the reasons.

[97] *Op.cit.*, point 12 of the reasons.

[98] T 604/04 (*PF4A receptors/GENENTECH*), point 5 of the reasons.

[99] T 1329/04 (*Factor-9/JOHN HOPKINS*), point 12 of the reasons.

[100] T 604/04 (*PF4A receptors/GENENTECH*), point 6 of the reasons

its structure, “the assumption (or “educated guess”) made in the patent application is plausible.”[101]

The Board goes on to say that the claimed receptor protein “cannot be seen as a mere tool for research undertaken for its own sake or in the quest to provide industrially applicable matter, but rather as a product with a plausible application in an industrial (medico-pharmaceutical) activity.”[102]

Thus, it follows that if a substance is considered to be of great importance for the advancement of new therapeutic agents, it might be permissible not to have clearly defined its function at the time the patent application is filed.

#### *3.4.1.2 Required evidence*

According to literature, establishing the subjective “at least plausible” test, sprouted many new questions. A central one of which, is when the EPO considers an invention as sufficiently complete to be able to carry out an examination of the fundamental criteria for patentability.[103] This is, of course, closely linked to questions that are essential in order to determine the most opportune time to file a patent application in the European “first to file” system The first of which being what data must be provided to sufficiently prove that the requirement is satisfied.

Article 83 EPC states that “[t]he European patent application shall disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.” This requirement is routinely assessed by the EPO, and often in relation to the assessment of Article 57 EPC.

[101] T 898/05 (*Hematopoietic receptor/ZYMOGENETICS*), point 27 of the reasons.
[102] *Op.cit.*, point 31 of the reasons.
[103] See Minssen 2008, p. 359

According to T 898/05 (*Hematopoietic receptor/ZYMOGENETICS*), function of a protein can be at three different levels:

> "i) the biochemical activity of the protein (protease, endonuclease, ion channel or pump, etc.), i.e. its molecular function; ii), the function of the protein in cellular processes (apoptosis, secretion pathway, etc.), i.e. its cellular function; and iii) the influence of those cellular processes within a multicellular organism, i.e. in a general and more complex network with a multicellular organism (cancer, inflammation, immune responses, etc.), this being its biological function in a broad sense."[104]

The biological function and the concrete benefits that followed from it, were in this case clearly disclosed.[105] Even though the details of the biochemical activity and cellular function of the protein had not been explained in the application, they could be directly derived from the disclosed experiment results.

It thus follows from this decision that the disclosure of function on one of the three levels, might in itself be sufficient to satisfy the requirement of industrial application, even if the other levels of function have not been elucidated.

Perhaps the most pressing question regarding the evidence required to support the claimed industrial application, is whether computer-assisted sequence data is sufficient, or if traditional wet-lab experiments are necessary.

The use of computer-assisted methods is becoming more common in research, and the importance of traditional wet-lab experiments may be declining, at least in the early stages of research and development. There will, of course, always be a need for *in vitro* and *in vivo* testing of new pharmaceutical inventions before they are brought to market in order to ensure that they are safe and have an appropriate efficacy. The actual functionality,

[104] T 898/05 (*Hematopoietic receptor/ZYMOGENETICS*), point 29 of the reasons.
[105] *Ibid*.

however, may conceivably be determined almost exclusively by computer simulation in the not too distant future.[106]

It seems clear from the case law, however, that there is still some reluctance to acknowledge industrial applicability when the proposed functions are based solely on *in silico* analyses.

In T 898/05 (*Hematopoietic receptor/ZYMOGENETICS*), the Board concedes that the structural properties of a protein may be derived from the gene sequence encoding it, but points out that the function cannot necessarily be determined in this manner. It is stated that "[t]he fact that the putative function of the Zcytor1 receptor was assigned in the examples based on computer-assisted methods, rather than on the basis of traditional wet-lab techniques, does not mean that it has to be automatically disregarded or excluded from a careful and critical examination".[107] The Board goes on to say that the "probative value" of evidence stemming from computer-assisted methods, must be "examined on a case-by-case basis regarding the nature of the invention and the prior art relating hereto".[108]

Thus, it follows that although *in silico* experiments certainly are permissible as evidence supporting a purported function, the weight carried by such experiments must be determined considering the nature of the invention (e.g. the complexity of the biological processes it is thought to affect or the importance of identifying new substances in the field) and the prior art relating to the area of the invention. If, for example, the prior art makes it clear that structure and functionality are closely related, a high degree of sequence homology with a substance of known function will indicate that the claimed substance also will be able to perform these functions.[109]

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[106] See Han van de Watermeemd and Eric Gifford, "ADMET in silico modelling: towards prediction paradise?" *Nature Reviews Drug Discovery*,2003 pp. 192-204. Also: Kelly Rae Chi, "Revolution dawning in cardiotoxicity testing", *Nature Reviews Drug Discovery*, 2013 pp. 565-567.

[107] T 898/05 (*Hematopoietic receptor/ZYMOGENETICS*), point 22 of the reasons.

[108] *Ibid*.

[109] *Ibid.* See also T 1165/06 (*IL-17 related polypeptide/SCHERING*), point 25 of the reasons: "The sequence information provided in the application with respect to the presence in IL-174 of the characteristic cysteine spacing of the IL-17 cytokine family makes it plausible that

It also seems that the threshold for regarding *in silico* results as sufficient is lowered when the substance is thought to be of major importance for research. This is the case in T 604/04 (*PF4A receptors/GENENTECH*), where the Board found that the importance of simply discovering new members of the PF4A chemokine receptor family was considered to be more important than to actually discover their specific functions.[110]

A higher threshold for computer-assisted homology studies supporting industrial applicability is set in T641/05 (*GPCR-like receptor/PHARMACIA*). The application in this case covered several slightly modified clones of CEGPCR1, a GPCR-like receptor[111] identified in the invertebrate *Caenorhabditis elegans*, that shared 89.6% sequence identity with AC7.1, a previously known GPCR-like receptor. This high degree of homology did, according to the applicant, indicate that the claimed clones would have the same applications as AC7.1, these being antibody and ligand binding and mediation of signal transduction.[112]

The Board noted that the evidence of function was based only on sequence homology analyses done with CEGPCR1, and that the protein was described as "tending to fall" into a group of known invertebrate neuropeptide receptors "closely related to a vertebrate family of receptors". There was also no distinction made between the reference sequence of CEGPCR1 and the specific sequences of the clones,[113] and it was well known that various GPCRs could have vastly different properties; some might not even have any activity at all.[114]

Because the patent was sought for several genes and their corresponding polypeptides, and their functions were based, solely or for the most part, on sequence homology studies, such

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this polypeptide may belong to this family and have biological activities similar to those of the other family members known at the filing date".

[110] T 604/04 (*PF4A receptors/GENENTECH*), points 17 and 18 of the reasons.

[111] G-Protein Coupled Receptors (GPCR) are transmembrane receptors that sense molecules outside the cell and activate inside signal transduction pathways and cellular responses, through the (guanine nucleotide-binding proteins) G-proteins, which act as molecular switches (See Nelson and Cox, 2013 pp. 435-436).

[112] T 641/05 (*GPCR-like receptor/PHARMACIA*), point XIII of the summary of facts and submissions.

[113] *Op.cit.*, point 10 of the reasons.

[114] *Op.cit.*, point 11 of the reasons.

studies should be provided for each of the claimed sequences. This is especially true where minute alterations in structure can lead to large changes in functionality.[115]

The Board found that no concrete information about applicable functions could be derived directly from the description or the prior art, and in conclusion stated that "[a]lthough, under certain conditions, the board is well prepared – following the case-by-case approach adopted in decision T 898/05 (*supra*) – to acknowledge a possible function based on computer assisted methods … in the present case the probative value of these (sequence homology) methods is completely lacking for the reasons set out above."[116]

It is clear then, that computer-assisted *in silico* experiments can be considered as sufficient evidence for industrial applicability to be acknowledged. This is, however, dependent upon the nature of the invention and the probative value of the results, which must be determined on a case-by-case basis.

#### *3.4.1.3 Required quality of the submitted evidence*

##### 3.4.1.3.1 Required quality of evidence in general

As it has been established what evidence must be submitted to support the purported industrial applications of an invention, the level of quality expected from this evidence must also be determined. Is it, for example, sufficient to plausibly demonstrate analogy between the claimed product and a substance of known function? And if such analogy is sufficiently proven, will it be adequate to provide a list of functions performed by the homologous substance?

It is abundantly clear from the case law that a way of exploiting the invention must be disclosed in the patent application. As seen above in 3.4.1.2, however, it follows from T 898/05 (*Hematopoietic receptor/ZYMOGENETICS*), that it may be sufficient to provide a function at one of three levels (molecular, cellular or biological) in order to satisfy the requirement of Article 57 EPC.

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[115] T 641/05 (*GPCR-like receptor/PHARMACIA*), point 11 of the reasons.
[116] T 898/05 (*Hematopoietic receptor/ZYMOGENETICS*), point 14 of the reasons.

In this case, the board found that the biological function was clearly disclosed. The applicant had performed tests showing that agonist ligands of the claimed receptor caused cell-mediated immunity and lymphocyte proliferation, while antagonist ligands caused suppression of the immune system.[117] Even though the molecular and cellular mechanisms behind this were not provided in the results, the Board found that they could be derived from the submitted evidence.

It can be inferred from this decision that corresponding ligands should be disclosed if the claimed substance is a receptor and vice versa. If function on a molecular, cellular and/or biological level can be derived from the interactions between ligands and receptors, this will then be sufficient to satisfy the requirement of industrial applicability.

This also follows from the decision in *ICOS/Seven transmembrane receptor*, where the opposition division found that the requirement for industrial application was not satisfied, because the uses proposed in the specification were based on a purported function of the V28 protein as a receptor. This function was, however, "not sufficiently disclosed in the specification".[118] It is stated that even if a putative function of a protein is disclosed along with a way of verifying this function, this is not "necessarily adequate to sufficiently disclose the function of the protein."[119] When the claimed protein is a purported receptor, a ligand capable of binding to the receptor must also be disclosed. Because no ligand was disclosed in the application, proposed uses were considered "speculative, ie are not specific, substantial and credible and as such are not considered industrial applications."[120]

It seems clear, therefore, that not only is it necessary to disclose a way in which the invention may be exploited in industry, but the disclosed application must also be based on sound, scientific evidence. Mere speculation will not be sufficient to satisfy the requirement of industrial application.

[117] T 898/05 (*Hematopoietic receptor/ZYMOGENETICS*), point 31 of the reasons.
[118] *ICOS/Seven transmembrane receptor*, point 9 (i).
[119] *Op.cit*., headnote
[120] *Op.cit*., point 9 (i)

Disclosing a clearly defined function is not always absolutely necessary, however. As seen above in 3.3 the Board in T 604/04 (*PF4A receptors/GENENTECH*) found that if the claimed product is of such significance to the advancement of research in the field that the mere identification is considered more important than actually determining a function.[121] There can, however, be little to no doubt that the claimed substance in fact has the purported features.

In T 18/09 (*Neutrokine alpha/HUMAN GENOME SERVICES*), the application in question was for a gene sequence encoding Neutrokine-α, a member of the TNF ligand superfamily.[122] The patent had been contested, on grounds of, *inter alia*, lack of industrial applicability.

The patent application relied, for the most part, on tissue expression data to prove that Neutrokine-α was in fact a member of the TNF ligand superfamily, as other members were known to be expressed in lymphomas. The specification also provided an undisputed structural identification of Neutrokine-α as a member of the TNF ligand superfamily and disclosed further relevant technical data, fully in line with the properties expected of a member of this superfamily. In particular, the specification disclosed the tissue distribution of Neutrokine-α mRNA[123] expression using the gene sequence encoding the protein as a cDNA[124] probe, and reported the expression of Neutrokine-α in activated T-cells.[125, 126]

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[121] T 604/04 (*PF4A receptors/GENENTECH*), points 17-18.

[122] The TNF (Tumor Necrosis Factor) family, is a group of cytokines that can cause apoptosis (programmed cell death). The TNF ligand superfamily is a family of ligands that bind to and consequently affect TNF receptors. Known to be expressed in lymphomas, and are therefore widely used in the diagnosis and treatment of lymphomas (see Hans Jürgen Gruss and Steven K. Dower, "Tumor Necrosis Factor Ligand Superfamily: Involvement in the Pathology of Malignant Lymphomas", *Blood*, **85** (12), 1995 pp. 3378-3403).

[123] mRNA: messenger RNA, an intermediary, carrying genetic information from one or a few genes to a ribosome, where the corresponding proteins can be synthesised (see Nelson and Cox, 2013 p. 273).

[124] cDNA: complementary DNA, a DNA strand complementary to an mRNA template, used to prepare synthetic DNA (see Nelson and Cox, 2013 p. 273).

[125] T 18/09 (*Neutrokine alpha/HUMAN GENOME SERVICES*), point 24 of the reasons.

[126] T-cell: "a type of small antigen-specific lymphocyte originating in thymus (in mammals) and present in secondary lymphoid tissues (e.g. lymph nodes, spleen) and blood, and which is involved in cellular immune reactions and aiding the production of antibodies" (*Henderson's Dictionary of Biological Terms*).

The Board states that because it was known from the prior art that a common feature of all members of the TNF ligand superfamily, is expression in activated T-cells, and ability to co-stimulate T-cell proliferation, "no serious doubts can be cast on this explicit additional information. Nor can this information be taken as a mere theoretical or purely hypothetical assumption."[127]

Although there was no doubt that members of the TNF superfamily may have many varied functions, and that further research definitely would be needed to fully explicate all functions of the protein, all the functions enumerated for members of the superfamily were, according to the Board, actually quite likely.[128]

It follows from the decisions cited above, that it is not absolutely necessary to provide experimental proof of a way in which the invention can be exploited in industry at the time the application is filed. Where the invention is *conclusively* proven (e.g. by structural homology or tissue expression data) to be a member of a family of substances that, with few exceptions, are known to have therapeutic effects, and it is probable that this is the case also for the claimed, a list of functions linked to other members of the family may be sufficient.

#### 3.4.1.3.2 Required quality of *in silico* evidence

As mentioned above, *in silico* experiments are rapidly becoming more prevalent in pharmaceutical research and development. And while it is clear that such evidence may be accepted as the main proof supporting the purported functions of an invention, it must still be determined what quality requirements are set for evidence stemming from computer-assisted analyses.

It follows from T 898/05 (*Hematopoietic receptor/ZYMOGENETICS*) that the "probative value" of *in silico* evidence must be assessed on a "case-by-case basis". The Board points out that the case law suggests that a protein could be considered as being industrially applicable

[127] T 18/09 (*Neutrokine alpha/HUMAN GENOME SERVICES*), point 24 of the reasons.
[128] *Op.cit*., point 23 of the reasons.

despite the patent application not disclosing sufficient experimental data. The Board refers to T 338/00 (*Multimeric receptor/SALK INSTITUTE*) and T 604/04 (*PF4A receptors/GENENTECH*), where the industrial applicability could be derived from the description when seen in combination with the general knowledge in the field.[129]

It is noted in the decision that the claims, through use of computer-assisted *in silico* analyses, disclosed several features related to the structure of the protein, that indicated Zcytor1 being a part of the hematopoietic receptor family[130] and the wider cytokine receptor superfamily. It is also pointed out that the application showed large scale Zcytor1 expression in immune cells and that the therapeutic applications were described for agonist and antagonist ligands of the protein. These data indicated important functions involved in the immune system, and possible applications in the development of therapeutic inventions.[131]

The Board found that because the structural features discovered by computer-assisted methods could be linked to the purported functions, and evidence showed that the protein was expressed in various human tissue, it was very likely that the protein indeed was a member of the hematopoietic receptor family. It is stated that:

> "Although the details of the biochemical activity and the cellular function of the Zcytor1 receptor have not been elucidated in the application, the (therapeutic) treatments directly derivable from the biological function identified by the computer-assisted method cannot be considered to be so "vaguely defined" that they do not suggest any therapeutic or diagnostic use. On the contrary, the treatments referred to in the application are specifically in relation to the function plausibly attributed to the molecule, and are in the areas of rheumatoid arthritis, multiple sclerosis, diabetes mellitus, etc. In this respect, this case differs from that of decision T 870/04

[129] T 898/05 (*Hematopoietic receptor/ZYMOGENETICS*), points 11 and 12 of the reasons.
[130] Hematopoietic receptor: receptors involved in haematopoiesis, the development of blood cells from stem cells (*Henderson's Dictionary of Biological Terms*).
[131] T 898/05 (*Hematopoietic receptor/ZYMOGENETICS*), point 21 of the reasons.

(*supra*) where no clear role for the claimed molecule was identified (cf. point 10 *supra*)."[132]

The application did not disclose the percentage of identity with other members of the family, or describe specific ligands. Nevertheless, the Board found that because earlier research indicated that members of the haematopoietic receptor family generally had analogous biological features and functions,[133] it was highly probable that the Zcytor1 receptor would perform similar functions.

The opposite conclusion was reached in T 1452/06 (*Serine protease/BAYER*). Here, the application covered a DNA sequence encoding a protein related to mouse epithin,[134] "expected to be useful for the same purposes as previously identified proteases … particularly useful for treating cancer and COPD".[135,136] The basis for these therapeutic indications, was the assumed role of the serine protease activity of the protein in the degradation of the extracellular matrix. The Board quickly concluded that in order for the "claimed subject-matter to fulfil the requirement of industrial application the purported serine protease activity of the polypeptide … is essential."[137]

However, the Board could not see that any experimental evidence had been presented in the application that showed the protein having serine protease activity. Neither was there evidence to support that the screening methods and therapeutic indications based on the purported activity could in fact be achieved with the claimed protein. According to the Board, the evidence presented was largely speculative and based on computer-assisted

[132] T 898/05 (*Hematopoietic receptor/ZYMOGENETICS*, point 31 of the reasons
[133] *Op.cit.*, point 27 of the reasons.
[134] Epithin is a serine protease, a class of enzymes that cleave peptide bonds in proteins, and are involved in several biological functions, including digestion, immune responses and reproduction. Epithin has also been shown to be involved in various cancer cell lines, and is therefore interesting in cancer treatment research. (See Hyo S. Lee et al., "Epithin, a target of transforming growth factor-beta signalling, mediates epithelial-mesenchymal transition", *Biochemical and Biophysical Research Communications,* 2010 pp. 553-569 (p. 553)).
[135] COPD: Chronic obstructive pulmonary disease.
[136] T 1452/06 (*Serine protease/BAYER*), point 3 of the reasons, referencing page 12, lines 10 to 12 of patent application 01964964.9 – Human epithin-like serine protease).
[137] T 1452/06 (*Serine protease/BAYER*), point 3 of the reasons.

homology studies of mouse epithin, which was only a "**putative** serine protease" (emphasis by the Board).[138] Regarding the presence of both serine and histidine active site signatures (which, according to a study presented in the application, made the probability of the protein being a member of the trypsin family of serine proteases 100%), it is stated that "[w]hereas the presence of these signatures might well be **necessary** for serine protease activity, these signatures are certainly not **sufficient** for a polypeptide to be functionally active" (emphasis by the Board).[139] It was highlighted that the disclosed polynucleotide was only a partial sequence of a gene that was similar to that encoding epithin, and that not all members of the serine protease family have the same biological functions. Consequently, the Board concluded that the computer-assisted studies were based on information far too incomplete to allow credible assumptions to be made regarding the function of the protein.[140]

This was also the conclusion in T 1109/10 (*Hydroxylases/LEXICON*). In this case, the application covered four proteins assumed to function as tryptophan hydroxylases,[141] "involved in a rate-limiting step in the biosynthesis of neurologically active compounds, including serotonin".[142] Because of this assumed function, the claimed proteins were expected to be useful in identification and development of pharmaceuticals for behaviour modification.[143]

The Board found that the description was severely lacking in evidence to support the claimed function of the proteins. It is stated that "[t]he fact that two proteins share a certain structural similarity does not automatically imply that they have the same enzymatic activity."[144]

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[138] T 1452/06 (*Serine protease/BAYER*), point 7 of the reasons.
[139] *Op.cit.*, point 8 of the reasons.
[140] *Op.cit.*, point 17 of the reasons.
[141] Hydroxylases are enzymes involved in hydroxylation, a chemical process which introduces a hydroxyl group into an organic compound. This process can convert lipophilic compounds into hydrophilic products, and is thus important in detoxification, as hydrophilic compounds are more easily secreted (see e.g. Nelson and Cox, 2013 pp. 798-799).
[142] T 1109/10 (*Hydroxylases/LEXICON*), point 3.1 of the reasons.
[143] *Op.cit.*, point 3.2 of the reasons.
[144] *Op.cit.*, point 4 of the reasons.

The proposed functions were based solely on amino acid sequence comparison, and the closest prior art had not presented any correlation between protein structure and tryptophan hydroxylase activity. A high degree of homology did therefore not give sufficient reason to assume that the claimed protein would possess the same functions as other hydroxylases.[145] As a result, industrial applicability could not be acknowledged.

In T 1165/06 (*IL-17 related polypeptide/SCHERING*), industrial applicability was acknowledged on the basis of sequence homology studies. In this case, the claim covered a polypeptide, IL-174, that showed significant sequence homology with the cytokine CTLA-8 (IL-17), which has been shown to function in controlling physiology, development and differentiation of mammalian cells. It was therefore assumed that the claimed proteins would be useful in mediating a variety of responses characteristic of cytokine signalling.[146]

In a very brief assessment of the requirement of industrial applicability, the Board states that because the sequence information clearly showed the presence of markers characteristic of the IL-17 cytokine family, it was "plausible that this polypeptide may belong to this family and have biological activities similar to this of the other family members".[147] This, held together with the confirming post-published documentation supplied by the applicant, meant that the requirement in Article 57 EPC was satisfied.

Regarding an actual quantification of the quality required, there are few examples of any more or less exact threshold in the case law.[148] According to a survey done by the Trilateral

[145] T 1109/10 (*Hydroxylases/LEXICON*), point 3.2 of the reasons.
[146] The IL-17 family of cytokines has been shown to be especially important in host defence and inflammatory diseases (see Wei Jin and Chen Dong, "IL-17 cytokines in immunity and inflammation", *Emerging Microbes and Infections*, 2013 pp. 1-5).
[147] T 1165/06 (*IL-17 related polypeptide/SCHERING*), point 25 of the reasons.
[148] See e.g. T 604/04 (*PF4A receptors/GENENTECH*), where 85% homology is accepted as sufficient (point 10), T 1329/04 (*Factor-9/JOHN HOPKINS*) where it is stated that members of a given subgroup of the TGF-β superfamily had between 70% and 90% homology (point 8), and T 1109/10 (*Hydroxylases/LEXICON*), where 71% homology was not sufficient to establish that a new human tryptophan hydroxylase had been identified (point 4).

Co-operation,[149] however, homology data will not be accepted by the EPO if the homology is below 55%, while 80% could be sufficient if the assay is done across the whole sequence and not just a restricted region.[150]

So, although there is no doubt that the EPO does allow results from computer assisted *in silico* studies as the main evidence in support of industrial application, there cannot be much doubt surrounding the value of the evidence. First of all, it seems that there needs to be a clear and definite correlation between the structure of the protein and its function. If this is evident from the general knowledge in the field and the prior art, a *high* degree of homology with a protein with a known function may be sufficient. If the family of protein the invention fits into is known to have many varied functions, further proof of function on a cellular or biological level may be required.

Also, if the claimed protein is thought to function in complex systems where many other substances are operative and affecting each other, more substantial evidence may be required. In such systems, it is less likely that the protein will carry out the exact function that the structure indicates, as it may e.g. act synergistically with one or more of the other substances in the system.

### 3.4.2 Weight of evidence submitted after the filing date

According to Rule 42 (1) (f) EPC, the "way in which the invention is industrially applicable" should be explicitly disclosed in the description. It is also abundantly clear from the case law that the assessment of industrial application, and indeed patentability in general, should be done on the basis of what is disclosed in the patent application.

[149] The Trilateral Co-operation is a cooperation between the EPO, the Japan Patent Office and the United States Patent and Trademark Office (USPTO), processing the majority of all patent applications filed worldwide (See trilateral.net).

[150] Trilateral project B3b – Trilateral Project B3b: Comparative study on biotechnology patent practices; Theme: Nucleic acid molecule-related inventions whose functions are inferred based on homology search (cases 9 and 10). Full text at http://www.trilateral.net/projects/biotechnology/mutual.pdf (last accessed 30 May 16).

This follows explicitly from the decision in T 1329/04 (*Factor-9/JOHN HOPKINS*), where the applicant had submitted post-published evidence that proved that the assumptions made in the application regarding function, were in fact correct. The Board, however, states that "[t]his cannot be regarded as supportive of an evidence which would have been given in the application as filed since there was not any."[151]

Moreover, the Board goes on to state that if post-published documentation was considered when no supportive evidence was disclosed in the application, this "would imply that the recognition of a claimed subject matter as a solution to a particular problem could vary as time went by."[152]

The industrial application should in other words be plausible at the filing date, by what is disclosed in the application.

There are, however, several examples of post-published evidence being taken into consideration. In T 898/05 (*Hematopoietic receptor/ZYMOGENETICS*), it is listed as one of the technical circumstances that should be included in the assessment of whether or not a "profitable use" can be derived from the description,[153] and it is stated that "the post-published evidence which confirms the preliminary finding and actually supports the conclusion, cannot be ignored."[154]

In T 1165/06 (*IL-17 related polypeptide/SCHERING*), the general assessment of Article 57 EPC is rather brief, as the Board "is convinced that the requirements […] are fulfilled".[155] It is, however, evident that the Board uses post-published evidence as confirmation that the functions disclosed in the application are plausible.

[151] T 1329/04 (*Factor-9/JOHN HOPKINS*), point 12 of the reasons.
[152] *Ibid*.
[153] T 898/05 (*Hematopoietic receptor/ZYMOGENETICS*), point 20 of the reasons.
[154] *Op.cit.*, point 24 of the reasons.
[155] T 1165/06 (*IL-17 related polypeptide/SCHERING*), point 25 of the reasons

Also in T 1329/04 it is stated that post-published evidence may be taken into consideration. It is however specified that "it may not serve as the sole basis to establish that the application solves indeed the problem it purports to solve."[156]

It seems clear then, that post-published evidence can be used to support the functions proposed in the application. However, such evidence will only be considered it if supports evidence that is actually disclosed at the filing date. If post-published evidence was allowed to be the main proof of the purported functions, it might lead to patent applications being handed in as soon as a new gene or protein is discovered, in essence reserving that area of research and gambling on finding evidence to support the supposed functions at a later date.

# 4 Conclusion

Because of the increasing importance of biotechnology and gene and protein based therapeutics, the number of patents filed for inventions in the field has been on the rise for the past few decades. Considering the substantial costs that are associated with research and development of new therapeutic agents, it is imperative for those involved to gain legal protection as early as possible to secure their investments.

The presence of an industrial application is effectively what separates a discovery from an invention. Defining how the requirement for industrial applicability should be understood, is therefore particularly important in order to determine the earliest point a patent application should be filed.

This paper has examined how the requirement for industrial application is interpreted for pharmaceutical and biotechnological inventions by the EPO Board of Appeal. The requirement is particularly important in this area, as the potential practical use of such inventions is not always obvious.

[156] T 1329/04 (*Factor-9/JOHN HOPKINS*), point 12 of the reasons.

From the evaluation of the Board of Appeal's interpretation of Article 57 EPC, it is first of all clear that the term "industry" should be construed in a broad sense, including all forms of industrial activity "that are carried out continuously, independently and for financial (commercial) gains".

This should not, however, be taken to mean that there is an absolute need for potential financial return to satisfy the requirement of industrial applicability. Rather, it should be understood to mean that an invention must have a *beneficial* use, constituting a concrete benefit to society, not just economic profit for the applicant.

The term "made or used in industry" should therefore not be interpreted literally for inventions in the biotechnological and pharmaceutical field. Since almost all such inventions can technically be reproduced ("made") and used in further research, a broad interpretation could lead to a system granting patents as hunting licences. Inventions must therefore have a clearly disclosed, *plausible* function that can be employed for e.g. diagnostic or therapeutic purposes. That the claimed substance can be used as a research tool, will rarely be sufficient to fulfil the requirement for industrial application, unless there is abundant evidence suggesting that the substance will be of great significance for the progression of research in the field.

Results from computer-assisted *in silico* experiments are permitted as evidence to support purported industrial applications, and it is not absolutely necessary to provide evidence from wet-lab tests. The "probative value" of *in silico* evidence must, however, be evaluated on a case-by-case basis. This means taking into account the nature of the invention (such as the complexity of the biological processes the invention is thought to affect, or the general importance of the discovery itself) and the prior art. There must be a clear correlation between gene sequence, protein structure and function on the molecular, cellular or biological level, though it is sufficient that a plausible function at *one* of these levels is disclosed. If the purported functions are based on homology with other substances, a high degree of homology is required.

Evidence submitted after the filing date *can* be taken into account, but such evidence must support what has been disclosed in the application as it is filed. A patent cannot be granted solely based on post-published evidence.

The examination presented in this paper suggests that EPO's technical Board of Appeal is attempting to be establish a stringent method for assessing the requirement of industrial application for biotechnological and pharmaceutical inventions, as there is consistently little deviation from existing case law.

In further research, a possible issue to investigate would be if the EPO sets a higher threshold for patenting biotechnological and pharmaceutical inventions than for inventions in other fields. The fact that the requirement for industrial application is not interpreted literally in such cases, as it theoretically should be according to Article 31 (1) of the Vienna Convention, certainly implies that a different standard is expected. Is there perhaps need for a separate requirement for inventions that are putative therapeutic agents? This is an interesting question, and one that should be answered as innovation in this field is becoming increasingly important for human health.

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