Patentability Requirements of Biotech Patents

Ulrich Storz

Abstract This chapter discusses patentability requirements in the two major patent jurisdictions, namely novelty, non-obviousness/inventive step, enablement/written description, best mode, and sufficiency of disclosure. Differences between Europe and the United States are highlighted, and practical implications are discussed with respect to the biopatent field.

Keywords Novelty · Obviousness · Enablement · Written description · Best mode · Industrial applicability · Inventive step · Sufficiency of disclosure · Biotech

1 Introduction

As discussed earlier in this book series, the allowance of a patent is subject to substantial examination. During this process, a number of tests is carried out, part of which are similar in the major patent jurisdictions, while others differ from one another substantially.

In the US patent system, the United States Code, Section 35 (USC 35) is decisive, whereas in the European patent system, the European Patent Convention (EPC) sets the standards. The following list gives an overview of the patentability requirements under USC 35 and EPC.

U. Storz (✉)
Michalski Huettermann and Partner Patent Attorneys, Speditionstrasse 21
40221 Duesseldorf, Germany
e-mail: st@mhpatent.de

U. Storz et al., *Biopatent Law: European vs. US Patent Law*,
SpringerBriefs in Biotech Patents, DOI: 10.1007/978-3-642-41293-6_1,

USC 35		EPC	
Requirement	Legal basis	Requirement	Legal basis
Novelty	§ 102	Novelty	Art. 54
Non-obviousness	§ 103	Inventive step	Art. 56
Enablement requirement	§ 112	Sufficiency of disclosure	Art. 83
Written description requirement	§ 112		
Best mode	§ 112		
		Industrial applicability and exclusion of methods of treatment and diagnosis	Art. 57, Art. 53 (c)

The present chapter will focus on a comparison of the tests as to novelty as carried out by the USPTO and the EPO to patents from the biotechnology discipline. Before doing so, however, some requirements specific to the two jurisdictions will be shortly addressed.

2 Foreplay: Requirements Specific to Either the EPC or USC 35

2.1 Industrial Application (Art. 57 EPC) and Exclusion of Methods of Treatment and Diagnosis (Art. 53 (c) EPC)

The test on industrial application as applied under Art. 57 EPC was initially used to block inventions which were related to therapeutic and diagnostic methods. The ratio behind this ban is that medical practitioners should not care about patents when deciding about practicing a given method of therapy or diagnosis. The industrial application standard is derived from the fact that, in Europe, medical professions are not considered to qualify as "industrial" or commercial. The exclusion of methods of treatment and diagnosis of humans and animals is furthermore specifically codified in Art. 53 (c) EPC.

2.1.1 Compound Patents Which Suffer from Insufficient Disclosure

Recently, Art. 57 has been used to block therapeutic compound patents which were filed at a stage where the applicant had no idea of the potential therapeutic use yet. Decision T870/04, which related to a patent application encompassing the hematopoietic cytokine receptor, and therapeutic antibodies binding thereto set forth that

> the mere fact that a substance can be made in some way does not necessarily mean that Art. 57 EPC is fulfilled, unless there is also some profitable use for which the substance can be employed.

However, this bar is very low. Technical Board's decision T0018/09 made this clear. The underlying patent EP0939804 assigned to HGS related to nucleic acids encoding for Neutrokine-α and an antibody that binds specifically to Neutrokine-α (now: BLyS or BAFF). Neutrokine-α is a member of the TNF-α superfamily, and was novel at the time of filing, but no experimental data were given as to therapeutic use, nor was a real antibody made. The applicant had only provided tissue distribution experiments of Neutrokine-α mRNA).

Nonetheless, the board judged that tissue distribution data suffice for industrial application and may be used to develop appropriate means for diagnosis and treatment. The key statement reflecting the board's opinion was as follows:

> In the board's judgment, the tissue distribution of Neutrokine-α mRNA disclosed in the patent-in-suit, in particular the expression of Neutrokine-α mRNA in B cell and T-cell lymphomas (…), provides in itself in the context of the disclosure a valid basis for an industrial application. The presence of Neutrokine-α in these lymphomas 8…] may be used to develop appropriate means and methods for their diagnosis and treatment based on the disclosure of the patent-in-suit.

The patent was thus maintained.

In corresponding proceedings in the UK, the Court of Appeal found the patent invalid for lack of industrial applicability, insufficiency, and obviousness, but the Supreme Court overturned this view, re-established industrial application and remanded the case. The Court of Appeal then established validity on September 5, 2012.

This decision thus defines the bottom line of real-world evidence applicants need today to meet the industrial application requirement in case they want to protect a new therapeutic compound. It is thus fair to say that, in today's examination policy, the industrial application requirement is easily met and has a practical role only when it comes to methods of treatment and diagnosis.

2.1.2 Medical Use Claims

Inventions that relate to a new indication for a pharmaceutical drug suffer from a conceptual problem, because, on paper, they relate to the use of said drug for a medical purpose and, as such, to a method of treatment which is exempt from patent protection under Art. 53 (c) EPC.

Under the last version of the EPC ("EPC 1973"), so-called Swiss-type claims were the only acceptable form of claiming a second medical use, because only under this wording an exclusion under then Art. 52 (4) EPC (now Art. 53 (c)) could be avoided. The Swiss-type claim language, which claimed the "Use of compound X in the manufacture of medicament Y for treatment of disease Z," was established by the Enlarged Board of Appeal (EBA) of the EPO in decision G5/83.

This format was a mere auxiliary construct to provide a commercial character to what otherwise would have been considered a mere therapeutic treatment. In decision G5/83, the EBA derived the novelty of such claims from their sole new feature, that is, the new pharmaceutical use of that known substance. The passage "in the manufacture of medicament," which is a common feature of all Swiss-type claims, was, however, never considered to have a restricting character. In fact, the scope of Swiss-type claims has always been defined as "purpose-bound compound protection."

Swiss-type claims are obsolete under the revised EPC (also called EPC 2000) and no longer allowable according to EBA decision G2/08, because the new Art. 54(5) EPC eliminates any legal uncertainty on the patentability of further medical uses.

The board stated that

> Article 54(5) EPC now permits purpose-related product protection for any further specific use of a known medicament in a method of therapy. Therefore, […] the loophole existing in the provisions of the EPC 1973 was closed. In other words "cessante ratione legis, cessat et ipsa lex", when the reason of the law ceases, the law itself ceases.

However, not only the necessity of using the Swiss-type format has ceased. The board also found them unallowable for future applications:

> Therefore, where the subject matter of a claim is rendered novel only by a new therapeutic use of a medicament, such claim may no longer have the format of a so called Swiss-type claim as instituted by decision G5/83.

The Swiss-type claim wording is today, replaced by a true second medical use wording, e.g., "Use of compound X for treatment of disease Z." As regards the scope of protection, this change has formal character only, because even before, Swiss-type claims were true medical use claims.

In the United States, such claim wording is not accepted, as "use" is not a claim category as provided by the US Patent Act.[1] Therefore, the corresponding claim wording should be as follows: "A process comprising administering a composition comprising compound X to a human in an amount effective for treating a disease Z".

2.2 Sufficiency of Disclosure (Art. 83 EPC)

2.2.1 General Issues

According to Art. 83 EPC, the application must disclose the invention sufficiently clear and complete to be carried out by a person skilled in the art. Case law

[1] 35 USC § 101: "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a Patent therefore."

interprets this requirement in a straightforward way. Technical Board's decision T94/82, for example, claims that

> The description must enable the person skilled in the art to obtain the claimed product described in it.

Technical Board's decision T0609/02 states that

> If the description […] provides no more than a vague indication of a possible medical use […], later more detailed evidence cannot be used to remedy the fundamental insufficiency of disclosure of such subject-matter.

The decision went on by stating that

> a simple verbal statement in a patent specification that compound X may be used to treat disease Y is enough to ensure sufficiency of disclosure […]. It is required that the patent provides some information in the form of, for example, experimental tests, to the avail that the claimed compound has a direct effect on a metabolic mechanism specifically involved in the disease, this mechanism being either known from the prior art or demonstrated in the patent per se.

In like manner, Technical Board's decision T1329/04 stipulates 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. Therefore, even if supplementary post-published evidence may in the proper circumstances also be taken into consideration, it may not serve as the sole basis to establish that the application solves indeed the problem it purports to solve.

One may from these decisions conclude that there is a disclosure requirement under the EPC, but it seems that the height of the respective bar changes from case to case.

2.2.2 Degree of Generalization and Non-working Examples

The disclosure requirement strives to ensure that a skilled person can reproduce the subject matter of the invention without undue burden. EPO examiners apply a quite liberal policy with respect to patent claims which comprise a generalized subject matter, provided the latter is novel, and a working example has been disclosed that falls under the scope thereof.

One example is thus usually sufficient to provide enablement, as long as no evidence exists that embodiments falling under the scope of the patent are not enabled. Accordingly, the guidelines for examination, which describe the general outlines of the EPO examination policy, set forth in Chapter F. IV that

> A claim in generic form […], may be acceptable even if of broad scope, if there is fair support in the description and there is **no reason to suppose that the invention cannot be worked through the whole of the field claimed**.

At the same time, the guidelines set forth that an examiner should

> raise an objection of lack of support only if he has well-founded reasons. Once the examiner has set out a reasoned case that, for example, **a broad claim is not supported over the whole of its breadth**, the onus of demonstrating that the claim is fully supported lies with the applicant Where an objection is raised, the reasons should, where possible, be supported specifically by a published document.

Thus, in case evidence exists that a patent claim is not supported over the whole of its breadth—in other words, a non-working example—the patent examiner may decide to narrow the scope of the claims to the very embodiment for which enabling data have been presented.

Such approach is oftentimes used by third parties, who file observations in the ongoing prosecution, or lodge an opposition, on the basis of a non-working example that also falls under the scope of said claim. It is in the nature of the examination process as such that these objections will mostly be raised by third parties, i.e., competitors, rather than by examiners, who have, generally speaking, no ambition to find non-working examples from literature, their search focus being directed at issues of novelty and inventive step.

One example for the increasing scrutiny with respect to sufficient enablement is given in Technical Board's decision T0601/05, which is related to a first-generation patent claiming human monoclonal antibodies (mAbs) that bind to human tumor necrosis factor α (TNF-α). The only method for the production of the claimed antibodies disclosed in the patent was the hybridoma technique developed by Köhler and Milstein (1975). In opposition proceedings, the board came to the conclusion that the hybridoma technique would not be suited to prepare high-affinity antibodies against TNF-α:

> Accordingly, human peripheral blood cells from a normal healthy individual cannot provide a route to high-affinity, neutralising antibodies to TNF. Thus, in the light of the evidence summarized above, the board is convinced that the method disclosed in the patent, even if combined with common general knowledge relating to this method, does not enable the skilled person to produce antibodies binding with high affinity to soluble TNF.

Because the claim language encompassed both high-affinity, neutralizing antibodies against self-antigens and low-affinity antibodies, the claim was found to be not sufficiently enabled by the specification.

The broadness of a given claim is thus limited not only by the prior art, but also by the existence of non-working examples falling thereunder.

2.3 Enablement and Written Description Requirement (USC 35; § 112)

Sufficiency of enablement and written description are two requirements under USC 35; § 112 which have often been mixed up even by patent professionals.

In March 2010, the US Court of Appeals for the Federal Circuit ("CAFC") issued a decision in case *Ariad vs. Eli Lilly*[2] which made clear that § 112 contains both (1) a written description requirement and (2) an enablement requirement and that both requirements differ from one another. Following this ruling, a patent specification

1. must describe the invention sufficiently so that one of the ordinary skills in the art would understand that the inventor possessed the subject matter claimed and ("written description requirement")
2. must teach one of the ordinary skills in the art how to make and use the invention ("enablement requirement")

The underlying case was related to Ariad's patent US6410516, which dealt with transcription factor NF-κB, and methods of reducing or altering its activity, yet without indicating how this could actually be done. The patent contained broad genus claims covering the use of all substances that achieve the desired result of inhibiting NF-κB activity. Although the specification recited the desired goal of reducing NF-κB activity, it did not disclose any working or even prophetic examples of methods that reduce NF-κB activity, and no completed syntheses of any of the molecules prophesized to be capable of reducing NF-κB activity.

In their request for *en banc* rehearing, Ariad claimed that there is no separate written description requirement in § 112, but that the description is just to identify what needs to be enabled. The CAFC rebutted this allegation by stating that:

> If Congress had intended enablement to be the sole description requirement of § 112, first paragraph, the statute would have been written differently.

The CAFC further noted that, in order to meet the written description requirement, more than merely repeating claim language in the specification is necessary:

> Generic claim language appearing in ipsis verbis in the original specification does not satisfy the written description requirement if it fails to support the scope of the genus claimed.

The court then specified what degree of evidence is required to meet the description requirement:

> The test requires an objective inquiry into **the four corners of the specification** from the perspective of a person of ordinary skill in the art. Based on that inquiry, the specification must […] show that the inventor actually invented the invention claimed.

The patent was thus found invalid for failure to meet the written description requirement. The decision fuels fears that the written description requirement discriminates against universities and start-up ventures that have their emphasis in basic research. These entities are under constant pressure to secure their results at the earliest possible date, and to the broadest possible extent, in order to publish

[2] 598 F.3d 1336, 1341 (Fed. Cir. 2010).

them or present them to potential licensees. A requirement for additional data in the future will increase the financial burden for these small or non-commercial entities.

In another groundbreaking case (*Centocor vs. Abbott*[3]), Centocor sued Abbott for patent infringement by selling adalimumab (Humira). Basis for the legal action was Centocor's patent US7070775, which relates to human antibodies to human TNF-α. The '775 patent is a continuation in part (CIP) of an earlier application by Centocor, which was related to chimeric antibodies.

However, said earlier patent predated a patent by Abbott related to similar subject matter. The case had generated broad public interest due to a record verdict in the first instance under which Abbott was sentenced to pay $1.67 bn in damages. On appeal, the decision was fully reversed by the CAFC only for lack of written description.

The CAFC considered that most claims of the '775 patent lacked written description, because the specification did not describe the claimed human antibody, nor an antibody with a human variable region, and concluded that

> "the scope of Centocor's right to exclude cannot over-reach the scope of its contribution to the field of art as described in the patent specification".

The claims on which Abbott had been sued were thus declared invalid.

Thus, while written description and enablement are not the same, the former focuses on the question whether the invention is described in such a way that the skilled person would understand that the inventor actually **possessed the invention**, while the latter relates to whether the invention is taught in such a way that the skilled person understands **how to make and use the invention**, both are important requirements, and should be considered with care, especially in cases where an application is meant to be filed at a very early stage, e.g., in order to secure an early priority date.

2.4 Best Mode (USC 35; § 112)

The recent amendment of US patent law under the America Invents Act (AIA), which went into effect on March 16, 2013, brought with it a removal of the so-called best mode requirement from the list of possible invalidity defenses.

The best mode requirement was considered a safeguard against the desire on the part of some people to obtain patent protection without making a full disclosure as required by the statute. This means that inventors were not allowed to disclose only what they knew to be their second-best embodiment, while retaining the best for themselves. The best mode requirement thus faithfully reflects basis principles of patent law, namely "quid pro quo" and "duty of candor and good faith."

In *Glaxo vs. Novopharm*,[4] the CAFC explained the essence of the best mode requirement as follows:

---

[3] 2010-1144 CAFC.

[4] 52 F.3d 1043, 1050 (Fed. Cir. 1995).

> The sole purpose of the best mode requirement is to restrain inventors from applying for patents while at the same time concealing from the public preferred embodiments of their inventions which they have in fact conceived. The best mode inquiry focuses on the inventor's state of mind at the time he filed his application […] The specificity of disclosure required to comply with the best mode requirement must be determined by the knowledge of facts within the possession of the inventor at the time of filing the application.

Further, the CAFC provided a comparison between best mode and enablement:

> Enablement looks to placing the subject matter of the claims generally in the possession of the public. Best mode looks to whether specific instrumentalities and techniques have been developed by the inventor and known to him at the time of filing as the best way of carrying out the invention. The **enablement requirement**, thus, looks to the **objective knowledge of one of ordinary skill in the art**, while the **best mode** inquiry is a subjective, factual one, looking to the **state of the mind of the inventor**.

As already envisaged, failure to disclose the best mode was removed, under the AIA, from the list of possible invalidity defenses to an infringement action. Further, failure to meet the best mode requirement will no longer be a factor in determining the priority date of a claim.

The USPTO has, however, advised examiners that objections addressing best mode requirement can still be raised during prosecution. The best mode requirement is thus still a very important requirement to meet.

3 Novelty and Inventive Step/Non-Obviousness: The Moving Target

The biotechnology disciplines underwent substantial advancements in the past 20 years. In antibody engineering and design, for example, the quick progress included the development of recombinant chimerization and humanization techniques, and the creation of libraries, display methods, and affinity maturation approaches. However, in a global knowledge society, a method that was cutting-edge technology yesterday may be an industry standard today, particularly with respect to technical disciplines that are strongly influenced by academic research. This is particularly true for biotechnology.

This situation is reflected in the increasing scrutiny patent authorities exhibit, e.g., with respect to antibody-related patent applications. The hurdles are steadily set higher, or, as the European Patent Office (EPO) puts it, "the bars are raised."

3.1 Novelty

Contrary to increasing requirements as to inventive step/non-obviousness, the respective authorities, including the EPO and the USPTO, seem to have recently

lowered hurdles with respect to the novelty requirement at least in some aspects. In others, the novelty bar has been raised, as will be discussed in the following.

3.1.1 Selection Inventions

Recent case law related to small molecules has strengthened the concept of selection inventions, which is established granting practice at the EPO already and which stipulates that the disclosure of a chemical class does not necessarily anticipate the novelty of an individual compound falling within this class. This is the so-called genus-species anticipation, according to which "a species anticipates the genus, whereas the genus does not anticipate a species".
This means, for example, that despite the fact that the racemate of a given structure is prior art, a patent related to only one enantiomer of said racemate may be considered novel and thus patentable in case the inventive step requirement is met (e.g., due to difficult resolution of the racemate). This view has been consented by courts in the UK, Germany, and the USA with respect to the (+)-enantiomer of Citalopram (decisions *Generics UK vs. Daichi*,[5] *BGH Escitalopram*,[6] and *Forest Labs., Inc. vs. Ivax Pharm., Inc.*).[7]

In another example, courts in all three countries agreed that a given compound, which falls within the scope of a general formula disclosed in the prior art, can be considered novel if it is not mentioned explicitly in the latter, but only by means of a Markush group in which some substituents are designated as R1–RX. Courts in UK, Germany, and the USA came to similar results in cases related to the anti-psychotic olanzapine (decisions *Dr. Reddy's vs. Eli Lilly*,[8] *BGH Olanzapin*,[9] and *Eli Lilly & Co. vs. Zenith Goldline Pharm., Inc.*).[10]

Translated to biomolecules, this means that, e.g., a sequence claim related to a second-generation antibody will be considered novel even if said claimed sequence is comprised in the similarity interval of a prior sequence disclosure (e.g., "SEQ ID No 1, or sequences having a similarity of >95 % with the former").

3.1.2 The Problem of Prior Art Applications Which are Post-published

According to a general principle, an invention is deemed novel if it is not known from the state of the art. The state of the art is composed of everything made

[5] (2008) EWHC 2413 (Pat), 2008 Bailii EWHC 2413.
[6] Xa ZR 130/07 (BPatG), 2009, GRUR 2010, 123.
[7] 501 F.3d 1263 (Fed. Cir. 2007).
[8] (2008) EWHC 2345 (Pat), 2008 Bailii EWHC 2345.
[9] Olanzapin, X ZR 89/07 (BPatG) 2008, GRUR 2009, 382.
[10] 05-1396, 05-1429, 05-1430, 2007 U.S. App. LEXIS 8750.

available to the public, e.g., by means of written description, before the priority date of a patent application.

Quite understandably, prior patent literature forms part of the state of the art, like any other type of literature. However, in most jurisdictions, patent applications are only made available to the public 18 months after their priority date. This can lead to a situation where, at the priority date of a given patent application ("application 2"), an earlier-filed patent application assigned to a third party exists already ("application 1"), which discloses similar or identical subject matter, but has not yet been published, and was thus unknown to the inventor of application 2. At the time of filing, the latter had thus reason to believe that his invention was novel—which it in fact was taking the above standard of availability to the public as a measure.

However, such constellation could lead to a situation in which the inventor of application 2 could obtain a patent on an invention that has already been described earlier in application 1 and assigned to another inventor.

In order to account for this problem, which could lead to double patenting, Art. 54 (3) EPC stipulates that the content of European patent applications filed prior to a given patent application, but published after the priority date of the latter, shall be considered as comprised in the state of the art.

Because of the fact that avoidance of double protection is the driving force behind this exception, its scope is restricted to assessment of novelty. Hence, under Art. 56 EPC such type of document (termed Art. 54 (3) document) shall not be considered in deciding whether the latter application relies on an inventive step. Thus, Art. 54 (3) EPC only applies for earlier-filed, yet post-published European patent applications (including PCT applications, provided they have been filed in an official language of the EPO), and prior art made available under this regulation can only be used for novelty objections.

Under the AIA, a similar regulation was recently introduced into US patent law. Contrary to the European regulation, however, the exception (1) applies to earlier-filed patent applications from any country and (2) prior art made available thereunder can be used for novelty objections and obviousness objections, again provided the alleged prior art document is subsequently published.

3.2 Inventive Step/Non-Obviousness

Probably due to the rapid technological progress in the biotechnology industry, arguments that were accepted in support of sufficient inventiveness in the past now may be rejected by the patent authorities as falling under the routine of a skilled artisan.

In view of the fact that technologies for the production of a human antibody against a given target are now state of the art (consider, e.g., native antibody libraries and phage display), the mere provision of a human antibody against a target the clinical implications of which are known would have difficulties to meet

the inventive step/non-obviousness requirement. In other words: The biotech industry is, in some way, a victim of its own success.

The test on inventive step, or non-obviousness, differs from the novelty test, in that an invention that passes the novelty test may still be objected as lacking inventive step, or being obvious, over the prior art. The ratio behind it is that embodiments may exist which, although formally novel, do not deserve exclusivity because they rely on a mere routine combination of features from the prior art, without any surprising effect or benefit emanating from that new combination.

Needless to say that such test is subject to large variances, because it suffers from conceptual problems, including subjectiveness, hindsight, and even language issues.

In order to anticipate obviousness objections during patent prosecution, applicants should add, to their applications, fallback positions, and experimental data, which can be used as a last resort to obtain patent protection for the actual compound or technology. Further, most of these data may also be used to meet the written description and enablement requirement (see above).

3.2.1 The European Approach

The test the EPO routinely applies is the so-called problem–solution approach, which follows a strictly predetermined line. The EPO has established this approach in an attempt to increase the degree of reproducibility in questions of inventive step (which otherwise would be subject to high variability, particularly in a trilingual system).

The approach consists of four steps:

1. Identify "closest prior art" (usually the prior art document which has most features in common with claimed subject matter) and determine the lacking features (the "delta")
2. determine the "objective technical effect" which said "delta" has
3. determine the "objective technical problem"—which is merely to achieve the objective technical effect starting from the closest prior art
4. "Could-Would test": Would (not only could) a skilled person in charge of solving the objective technical problem have come to the claimed solution by combination of the closest prior art document with another prior art document?

The "Could-Would test" thus seeks to determine whether, beyond the mere theoretical possibility that when combining two prior art documents one would have arrived at the claimed solution, a skilled person would actually have done so.

In Biotech, the preferred "Could-Would test" is the "Reasonable expectation of Success" test.

Practically, the problem–solution approach allows successful obviousness attacks only in case the "delta" between the claimed subject matter and the closest prior art is small, which means the latter must not lack more than one feature.

3.2.2 The US Approach

Under US law, the key features of the non-obviousness test have been laid out by the US Supreme Court in *KSR vs. Teleflex.*[11] In said decision, the court made, inter alia, the following statements:

> Obviousness requires more than a mere showing that the prior art includes separate references covering each separate limitation in a claim under examination.
>
> Rather, obviousness requires the additional showing that a person of ordinary skill at the time of the invention would have selected and combined those prior art elements in the normal course of research and development to yield the claimed invention.
>
> A person of ordinary skill at the time of the invention interprets the prior art using common sense and appropriate perspective.

The Supreme Court overturned an earlier decision by the CAFC and found that the latter had applied the so-called teaching-suggestion-motivation test (TSM) test in an overly rigid and formalistic way.

The Supreme Court made clear that, under the TSM test, a claimed invention is obvious when there is a teaching, suggestion, or motivation to combine prior art teachings. The teaching, suggestion, or motivation may be found in the prior art, in the nature of the problem, or in the knowledge of a person having ordinary skill in the art. The court, however, set forth that the TSM test is not the only rationale that may be relied upon to support a conclusion of obviousness.

In the earlier decision *Graham vs. John Deere*,[12] the Supreme Court had already defined the so-called Graham factors, according to which obviousness should be determined by looking at

1. the scope and content of the prior art;
2. the level of ordinary skill in the art;
3. the differences between the claimed invention and the prior art; and
4. objective evidence of non-obviousness

The latter are, for example, commercial success, long-felt but unsolved needs, and failure of others.

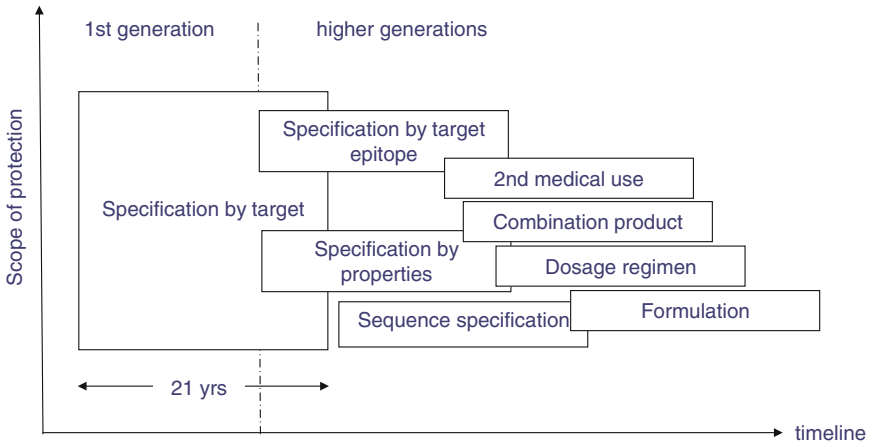
While the basic outline of these approaches shares some similarity with the problem–solution approach used by the EPO, there is the general perception that the latter is more formalistic, giving the examiners less room for interpretation. Further, under the problem–solution approach, an inventive step attack based on a combination of more than two prior art documents is unlikely to be successful, while USPTO examiners regularly object patent applications for obviousness in view of a combination of three or more prior art documents.

[11] 550 U.S. 398, 418 (2007).

[12] 383 U.S. 1 (1966).

3.2.3 The Situation in Therapeutic Antibodies

In therapeutic antibodies, which are one of the commercial success stories in biotechnology, different patent generations can be determined, all being derivatives of a first patent application which has a claim on a theoretical antibody against a new target. The following figure shows the most important categories of patent protection in therapeutics antibodies. Note that the units are arbitrary, and the actual order of the different categories may vary from case to case. Further, note that not in each case all categories are used.



Among these different types of protection, specification by target and specification by sequence are probably the two most important types. We will discuss inventive step issues with respect to these two categories in the following:

mAb Specification by Target: Background

Today, about 100 cellular targets are addressed by approved biopharmaceuticals, yet the spectrum of promising targets for new therapeutic mAbs is much higher (Overington et al. 2006). There is thus still room for the discovery of a new target and for the invention of a drug addressing said target.

In case an applicant specifies a new target in sufficient manner, and renders plausible a therapeutic effect of blocking said target, the EPO accepts claims related to a theoretical mAb against said target ("target claims"), even if the applicant has never actually made such mAb, or only made a polyclonal or murine monoclonal.

This position is, for example, demonstrated in Technical Board's decision T542/95, which related to antibodies against human TNF. The board argued that

> The prior art does not disclose the purification of the same hTNF (CT) as in the patent in suit. […]. Accordingly, the **presence of inventive step can be acknowledged** for the claims.

Contrary to USC 35; § 112, the EPC has no explicit written description requirement, and thus, "possession of the invention" is not a statutory requirement. EPO's ratio is that the skilled person has, by specifying the target, enabled the skilled person to make an antibody against said target by routine methods (Koehler Milstein, Phage display etc.). Therefore, it is considered a fair reward for the applicant of protein X to be granted a claim related to a theoretical antibody against said protein.

mAb Specification by Sequence: Background

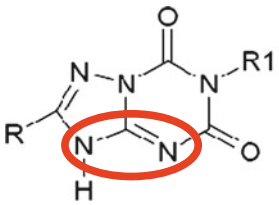
Another way to create patent protection for a second- or higher-generation antibody is to specify a sequence thereof ("sequence claims"). The scope of protection of such claim type is, on paper, pretty narrow, and issues of equivalence are so far unresolved, as no case law exists yet with respect to scope of equivalence of biosequence claims.

However, the European Medicines Agency (EMA) will most probably consider counterfeit products only as biosimilars (and thus eligible for facilitated approval) in case of an identical amino acid sequence. Thus, even if the scope of protection of an antibody sequence claim could be bypassed by exchanging one amino acid only, such approach is no option for biosimilar companies who want to take benefit from facilitated approval pathways. These companies thus have to wait until the patent expires. Thus, although theoretically narrow, structural claims can provide meaningful and strong protection for an approved antibody.

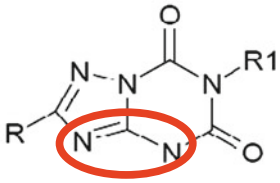
In antibody sequence claims, the EPO usually requires at least two variable chains (heavy and light), or all six CDRs to be recited in the claim. The ratio behind this requirement is that at least six CDRs, or the heavy and light chain, are needed for proper binding function. For single-domain antibodies or binding peptides, less can be sufficient if experimental evidence is provided.

In structural small molecule claims, it is established EPO case law that novelty more or less implies that the inventive step criterion is also met. Only in case a structurally similar molecule is prior art, and it was predictable that the modification which is subject to the patent has no negative effects, the EPO requires a "surprising effect" to meet the inventive step criterion.

For example, the following two compounds are not considered to be "structurally close," because of differences in the heterocyclic system:



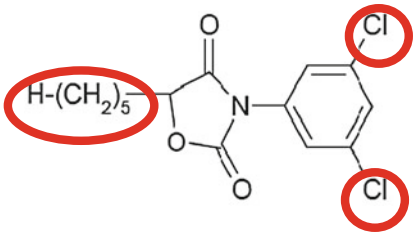
1A (prior art)



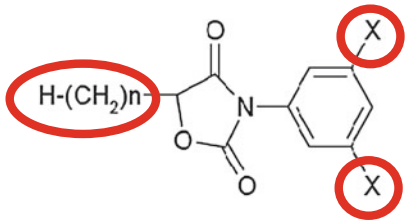
1B (novel)

Because both compounds are not structurally close, the EPO does not require compound 1B to exhibit advantages or surprising effects over compound 1A for being considered as being based on an inventive step.

In contrast thereto, the following two compounds are considered to be "structurally close," because the two ring systems are essentially the same.



2A (prior art)

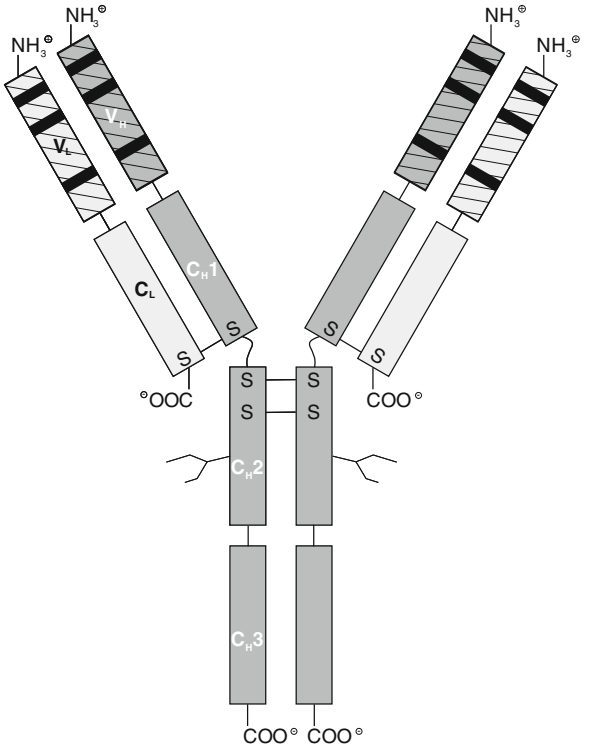


2B (novel), n = 2, 3

Hence, compound 2B has to exhibit advantages or surprising effects over those exhibited by compound 2A for being considered as non-obvious.

In contrast thereto, the EPO regularly requires, in structural antibody claims, that the applicant provides "surprising effects" over existing antibodies against the same target. Following an analogy to the examination policy in small molecules, the EPO stipulates that all IgG are "structurally similar," because they share the same backbone, in which, essentially, only the complementarity determining regions (CDRs) have been replaced according to the respective target.

The latter form, however, only a very small fraction of the entire structure of, e.g., an IgG antibody, as can be seen in the following figure (black bars show the CDRs):



The provision of "yet another antibody" against a known target is considered to be in the routine of the skilled person, because respective methods exist (phage display, affinity maturation, and the like). The EPO thus considers structural antibody claims which address a target already addressed by earlier antibodies as not inventive unless surprising effects are disclosed by the applicant—a policy which has been termed the "antibody sonderweg".

This position is, nowadays, established case law. In Technical Board's decision T512/94, the respective board states that

> Once a monoclonal antibody with essentially the same properties as desired had been isolated, the skilled person would consider the **isolation of another equivalent antibody as reasonably feasible**, if only by following the very same method.

In Technical Board's decision T735/00, the board concluded that

> If, however, there are no **unexpected effects achieved with a further monoclonal antibody** compared with a monoclonal antibody with essentially the same properties as desired the case law denies inventive step.

In Technical Board's decision T 735/00, the board had to decide about, inter alia, on the inventive step of the following claim:

> 1. A monoclonal antibody selected from the group consisting of monoclonal antibody CRP-1 obtained from hybridoma cell line CRP-1 (FERM BP-2873), monoclonal antibody CRP-2 obtained from hybridoma cell line CRP-2 (FERM BP-2874), monoclonal antibody CRP-3 obtained from hybridoma cell line CRP-3 (FERM BP-2875), and monoclonal antibody CRP-4 obtained from hybridoma cell line CRP-4 (FERM BP-2876).

The closest prior art disclosed two antibodies against CRP. The board came to the conclusion that the technical problem was to find an alternative mAb against CRP. Yet, 13 years after Köhler and Milstein, the board saw no merits in using this method to make an alternative antiCRP-mAb in the absence of any unexpected properties and revoked the patent in March 2004. The corresponding US patent US5500345 was yet granted 1996 with similar claims.

Criticism

It is extremely arguable whether this strict position is justified. Due to the more or less chaotic and unpredictable interplay between the amino acid residues in a peptide chain, the mere replacement of only a single amino acid residue can dramatically affect the affinity or specificity of an existing antibody.

The variable regions have about 120 amino acids, which makes 3.83×10^{41} potential variants.

Before this background, starting from a first-generation antibody with a given sequence, what expectation of success would a skilled person have to end up at the specific sequence of a given second- or higher-generation antibody?

The "antibody sonderweg" is also contrary to EPO's existing examination policy in other technical disciplines:

In Technical Board's decision T92/92, which related to a glide shoe, the board found that

> no ground can be seen why a novel, alternative solution to a known problem should be excluded from patentability for lack of inventive step for the reason that the problem has already been solved in a different manner.

In Technical Board's decision T467/94, which related to a pharmacological pyridinium composition, the board stipulated that

> the technical problem […] can be seen in the provision of further useful anti-ulcer agents. […] The question […] is whether the cited documents would have suggested [...] solving the […] technical problem in the proposed way.

Further, according to the guidelines of examination, Part C, Chapter IV, 9.8.2, a "technical problem" does not imply that the technical solution is an improvement over the prior art. Problem can be simply to seek an alternative to a known device or process. EPO's granting practice with respect to structural antibody claims is thus in conflict with established case law in other technical disciplines.

While target claim patents, toward which the EPO exercises a liberal examination policy, will oftentimes be used by target discovery companies and

universities, structural claim patents come into play once a specific mAb is developed for therapeutic use and are thus primarily used by pharmaceutical companies. While target discovery as such is definitely a costly matter, and deserves adequate patent protection, the development and approval of a new therapeutical mAb outranks the latter by orders of magnitude (DiMasi and Grabowski 2007). EPO's concept to (1) routinely grant functional claims on a theoretical antibody in case the target is novel, but to set (2) high bars with respect to structural claims on a second- or higher-generation antibody therefore seems to overcompensate target discovery companies and undercompensate pharmaceutical companies.

The fact that this policy is a mere logical continuation of EPO's policy when the first monoclonal antibody patents were filed, in which case patent claims related to mAbs that replace prior art polyclonal antibodies were rejected denied unless the former had surprising effects (see, e.g., Technical Board's decisions T36/90 and T499/88) provides cold comfort only.

Implications for the Therapeutic Antibody Industry

Structural antibody patents must be filed at a very early stage to avoid novelty problems. Oftentimes, one or more structurally defined lead candidates exist, but little is known about them beyond their sequence. Accordingly, functional characteristics of these lead candidates can only be determined at a later stage, i.e., through CROs.

If the EPO applies the above-described policy too rigidly, the successful patent prosecution of structural antibody patents may be put at risk. The development of new antibody therapeutics may thus become commercially unattractive at least in cases where the target is already known (i.e., second-generation antibodies), because, in the pharmaceutical industry, a patent is indispensable to protect R&D expenses. Otherwise, a newly approved antibody would soon become subject of generic competition.

However, the oft-cited "surprising effect" does not always have to be affinity. Other effects setting the subject antibody apart from prior art can also be used. Consider, e.g., clotting behavior, effector function, the target epitope to which the subject antibody binds, immunogenity, serum half-life, or stability.

Further, even if an applicant has no data with respect to these features at hand at the priority date, such data supporting a surprising effect can be submitted later on, even during prosecution, in case such data relate to features mentioned as such in the specification. For this reason, applicants should at least write a clause mentioning these features in a general fashion into the specification, to be able to react flexibly during prosecution.[13]

[13] Possible in the US and before the EPO, not possible in Japan and China.

3.2.4 The Policy of the USPTO

As regards target claim patents, the CAFC held in *Noelle vs. Lederman*[14] that the applicant did not provide sufficient support for claims to a human CD40CR antibody, because he failed to disclose the structural elements of human CD40CR antibody or antigen and was thus denied an earlier filing date. In fact, the earlier filing date related to an application which disclosed the mouse antigen mly, plus the ATCC number of the hybridoma cell secreting the mouse CD40CR antibody. However, quite remarkably, the court stated that

> Therefore, based on our past precedent, as long as an applicant has disclosed a "fully characterized antigen," either by its structure, formula, chemical name, or physical properties, or by depositing the protein in a public depository, the applicant can then claim an antibody by its binding affinity to that described antigen.

This decision has been confirmed in *Centocor vs. Abbott*,[15] in which the court argued as follows:

> While our precedent suggests that written description for certain antibody claims can be satisfied by disclosing a well-characterized antigen, that reasoning applies to disclosure […] where creation of the claimed antibodies is routine

The US position with respect to target claim patents is thus pretty much the same as that of the EPO. Accordingly, HGS's US-Patent 6,403,770, which corresponds to EP0939804 (that has eventually been allowed in Technical Board's decision T0018/09 and is discussed above), made this clear. The patent has been granted with the following main claim:

> 1. An isolated antibody or portion thereof that specifically binds to a protein consisting of an amino acid sequence of amino acid residues 1 to 285 of SEQ ID NO: 2.

The patent is still in force and has been and recommended for PTE by the DOH.

With respect to structural mAb claims, US case law seems not to require a "surprising effect" to accept non-obviousness. In the CAFC case *re Deuel*,[16] the court argued that

> the existence of a general method of isolating cDNA or DNA molecules is essentially irrelevant to the question whether the specific molecules themselves would have been obvious, in the absence of other prior art that suggests the claimed DNAs.

The USPTO Manual of Patent Examining Procedure ("MPEP") puts it similarly (see Section 2144.09)

> The existence of a general method of gene cloning in the prior art is not sufficient, without more, to render obvious a particular cDNA molecule

---

[14] 355 F.3d 1343 (Fed. Cir. 2004).

[15] 2010-1144 CAFC.

[16] 51 F.3d 1552 (Fed. Cir. 1995).

Before this background, the often-made allegation that the EPO is more inclined than the USPTO to grant target claim patents is probably unjustified. However, as regards structural claim patents, the USPTO granting practice is in fact more liberal, as no surprising effect is required to establish non-obviousness/inventive step.

References

DiMasi JA, Grabowski HG (2007) The cost of biopharmaceutical R&D: is biotech different? Mange Decis Econ 28:469–479

Köhler GF, Milstein C (1975) Continuous cultures of fused cells secreting antibody of predefined specificity. Nature 256:495–497

Overington JP, Al-Lazikani B, Hopkins AL (2006) How many drug targets are there? Nat Rev Drug Discov 5:993–996