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From Clones to Claims

A Handbook on Patenting Biotech and Biopharmaceutical Inventions in the European Patent Office and on Enforcing such Patents

by

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7.1.1 The Genentech polypeptide expression cases T 292/85, T 293/85 and T 794/94, EP-B1 1 929

7.1.1.1 *T 292/85 of January 27, 1988*

This decision was a landmark decision for the question of enabling disclosure in biotechnology inventions. It deals with an appeal filed by an Applicant whose application was rejected by the Examining Division for lack of enabling disclosure.
The Technical Board set aside the Examining Division's decision and granted a patent, EP-B1 1 929, on the basis of the following claim 1:

> A recombinant plasmid suited for transformation of a *bacterial host* comprising a *homologous regulon* and, the heterologous DNA encoding a *functional heterologous polypeptide or intermediate therefor*, said homologous regulon being arranged with said heterologous DNA so as to control transcription and translation of said heterologous DNA encoding said functional heterologous polypeptide or intermediate therefor, whereby on translation of the transcription product of the heterologous DNA in a suitable bacterium, the resulting expression product is said functional *polypeptide or intermediate* therefor *in recoverable form*.
> (emphasis added)

Obviously, the claim was solely composed of functional features for characterizing the recombinant plasmid to which it referred.

When rejecting the application, the Examining Division

> insisted that all embodiments in the claims must have been capable of being carried out by the skilled person at the priority date and in a repeatable manner without practising inventive skill. *No claims should rely on constituents which represent further inventions*…
>
> *Claims should, in effect, at least be limited to what is available at the priority date, i.e. known bacteria, plasmids and DNA relating to known polypeptides*. A process for the preparation of a human hormone could not be identically repeated since the source of the DNA in humans varied with the individual. *In general, no component should be defined in functional terms in this field of technology*.
> (emphasis added).

Recognizing the necessity of awarding worthwhile protection for biotechnology inventions and thus being able to rely on functional terms in corresponding claims, the Technical Board did not share the Examining Division's view but argued in great detail against it:

> 3.1. Components of the future
> 3.1.1 … According to the Examining Division this situation contradicts the suggested requirement that all embodiments within the claims should be reproducible at will by the skilled person without having to make an invention.
> 3.1.2 *There is, however, in the opinion of the Board, no such requirement in the European Patent Convention, nor is such principle established in normal patent practice within the Contracting States*. The suggested features in the claims are essentially *functional terms* in this particular context, in spite of structural connotations, and may cover an unlimited number of possibilities. It follows that the features *may generically embrace the use of unknown or not yet envisaged possibilities*, including specific variants which might be provided or invented in the future. This Board concurs with the decision of another Board (T 68/85–3.3.1., "Synergistic herbicides", OJ EPO 1987, 228) in which the possibility of using functional terminology in claims was approved *if "such features cannot otherwise be defined more precisely without restricting the scope of the invention"*

and their reduction to practice was not an undue burden. The Board sees no valid reason why this should not be equally true for the field of biotechnology as in other fields of technology.

…

3.1.4 The objection raised against the *terms "plasmid"* and *"bacteria"* that they are too broad since some of them rely on yet unavailable entities is untenable. The Board is of the opinion that this is *quite normal practice* in many technical fields where terms as "carriers", "resilient means", or "amplifying means" are commonplace and embrace new components, be they inventive or not….

3.1.5 The above examples show that the need for a fair protection governs both the considerations of the scope of claims and of the requirements for sufficient disclosure. *Unless variants of components are also embraced in the claims, which are, now or later on, equally suitable to achieve the same effect in a manner which could not have been envisaged without the invention, the protection provided by the patent would be ineffectual*. Thus it is the view of the Board that *an invention is sufficiently disclosed if at least one way is clearly indicated enabling the skilled person to carry out the invention*. Consequently, any non-availability of some particular variants of a functionally defined component feature of the invention is immaterial to sufficiency as long as there are suitable variants known to the skilled person through the disclosure or common general knowledge, which provide the same effect for the invention. *The disclosure need not include specific instructions as to how all possible component variants within the functional definition should be obtained*.

…

3.2. Inoperable components

3.2.1 Whilst the Board is satisfied that there are sufficient choices of bacteria available, and that there might be more suggested in the future, the question of non-operability of some bacterial variants may arise….

It is, therefore, also the view of the Board that *the unsuitability of some unspecified particular variants of a* functionally *defined component feature of the invention is immaterial* as long as there are suitable variants known to the skilled person through the disclosure or common general knowledge which provide the same effect for the invention. (emphasis added).

This decision was a decisive starting point for establishing a rather generous practice with respect to the allowable scope of claims in the field of biotechnology inventions; see, e.g., **T 293/85** (section 7.1.1.2, *infra*), **T 347/87**, **T 301/87** (section 7.1.2, *infra*), **T 19/90** and **T 242/92**.

7.1.1.2 T 293/85 of January 27, 1988

This decision relates to subject matter which is very similar to that of **T 292/85**, 7.1.1.1, *supra*. The Technical Board granted a patent, EP-B1 1 930, containing the following claim 12:

> 12. A recombinant plasmid comprising a homologous regulon, a DNA sequence encoding a desired specific heterologous polypeptide, a selective cleavage site and additional protein, and one or more termination codons, wherein the said DNA sequence is interposed in proper reading frame between said regulon and termination codon(s) such that a conjugate polypeptide comprising both the desired heterologous polypeptide and additional protein results from expression in a bacterium transformed with the plasmid, there being a selective cleavage site between the desired heterologous polypeptide and the additional protein.

The Technical Board pointed out that

> the disclosure need not include specific instructions as to how all possible component variants within the functional definition should be obtained.
>
> **T 293/85** at section 4.

Furthermore, the Technical Board concluded:

> Since the generalizations in the present case are based on the same factual background as in the Decision in T 292/85, the same conclusions must be drawn. No insufficiency with regard to the terms objected to arises therefore under Article 83 EPC.

T 293/85 at section 4.

7.1.1.3 *T 794/94 of January 15, 1999*

After grant of EP-B1 1 929, it was opposed by seven opponents. During the opposition proceedings the claims were amended several times but, nevertheless, the patent was revoked by the Technical Board at the end of the oral proceedings on September 17, 1998. What did the Technical Board lead to this opposite view? It was a series of lectures given by one of Patentee's scientists during which the expression of somatostatin as a fusion protein with ß-galactosidase was described in detail. Thus, the most important example of the patent suddenly belonged to the prior art. It was particularly this example on the basis of which Patentee had drafted the initially granted generic claim.

Claim 1 of Auxiliary Request II drafted as the last resort read as follows:

> 1. A recombinant plasmid suited for transformation of a bacterial host, wherein the plasmid comprises a homologous regulon and heterologous DNA, the heterologous DNA encoding a desired functional mammalian polypeptide or mammalian intermediate therefor, which is not degraded by endogenous proteolytic enzymes, the DNA being immediately preceded by a start codon and immediately followed by one or more termination or stop codon(s), whereby said desired functional mammalian polypeptide or intermediate therefor is neither preceded nor followed by additional protein, said DNA being positioned in proper reading frame with said homologous regulon between said regulon and the termination codon(s), whereby on translation of the transcription product of the heterologous DNA in a suitable bacterium, the resulting expression product is said desired functional mammalian polypeptide or mammalian intermediate therefor in recoverable form.

Thus, Patentee, in view of the prior art on fusion protein expression, now wanted to restrict the claims to non-fusion protein expression embodiments only. This, however, meant that the "only one way of carrying out the invention has to be disclosed" principle established by **T 292/85** was no longer applicable. For the claimed scope there was no actual example anymore. The patent only disclosed successful fusion protein expressions but indicated by way of experimental results that non-fusion expression products, such as somatostatin, would not be stable.

When assessing enabling disclosure of this claim drafted on the basis of no examples, the Board stated the following and revoked the patent:

> 3.4.3 As for the technical teaching that non-fusion mammalian proteins are stable upon expression provided they are sufficiently large, which the appellant maintains that the patent in suit conveys to the skilled person, the board, in spite of a close scrutiny of the whole application as filed, is unable to derive this technical teaching either explicitly or implicitly. The only deduction in relation to the somatostatin and insulin polypeptides mentioned that the skilled person can make, is that these require to be fused to some longer endogenous polypeptide if they are to avoid digestion. Nothing is said as to which, if any, mammalian polypeptide could avoid being degraded if DNA coding only for these is inserted as required by claim 1.
> In a different context (see section XI, *supra*), the appellant argued that the skilled person attending Dr Heyneker's presentation on the research results relating to somatostatin expression (OD51) would have viewed the endogenous β-galactosidase

protein as a protective carrier for the heterologous polypeptide (cf. the expression in document (111), last page: "burying somatostatin at the end of β-galactosidase") and that **no more than this** could have been deduced from this presentation. These considerations strengthen the board's view that the skilled person cannot deduce from the patent in suit more than the teaching that somatostatin and insulin require a long protective endogenous protein if they are to avoid proteolysis.

3.4.4 In view of the above finding, the board is unable to formulate any problem in relation to claim 1, for which it can be said that it has been solved by the novel information. It can also not be said that the actual contribution to the state of the art made by the disclosure of the patent in suit consists of providing experimental support for the direct expression of mammalian proteins, i.e., the technical contribution is not a new technique but the successful completion of an experiment known at a theoretical level from the prior art, as in the case dealt with in decision T 694/92 (OJ EPO 1997, 408). This is because the direct expression of mammalian proteins is not exemplified in the patent in suit. *Therefore, either the skilled person could make what is claimed in claim 1 already on the basis of the prior art, or both the prior art and the patent in suit contain insufficient information to realize what is claimed in claim 1. Thus claim 1 must fail either as the requirements of Article 83 EPC have not been fulfilled, or for lack of inventive step (Article 56 EPC). In the absence of clear evidence that the equivalent information provided by the prior art, or by the patent in suit, is insufficient to allow the skilled person to carry out the invention, the board finds that claim 1 lacks an inventive step.* The 2nd auxiliary claim request too has also to be rejected and the appeal dismissed. (emphasis added)

However, the decision did not at all allow the conclusion that from then on the disclosure of only one way of carrying out an invention would no longer have been sufficient.

7.1.2 *T 19/90, "Onco-mouse/HARVARD", and T 694/92, "Modifying plant cells/MYCOGEN"*

These are two decisions of fundamental importance when it comes to the assessment of enablement – and its correlation with the assessment of inventive step.

7.1.2.1 In **T 19/90** the application was filed on June 24, 1985. The Examining Division refused the application with decision of July 14, 1989 because it took the position that the pending claims were in conflict Articles 53(b) and 83 EPC. An appeal was lodged and allocated the file number **T 19/90**. The Technical Board gave its decision on October 3, 1990. After remittal of the case to the Examining Division for further prosecution, a patent was granted on May 13, 1992. Upon grant, seventeen oppositions were filed, predominantly based on the argument that the patent would be in conflict with the morality standards applicable under Article 53(a) EPC. Oral proceedings before the Opposition Division took place for the first time in November 1995. However, due to unfortunate circumstances, the composition of the Opposition Division changed so that oral proceedings had to be held again in November 2001. Eventually, there was a written decision dated January 16, 2003 against which several appeals were filed. This new appeal case was **T 315/03**. The Board gave its decision rather quickly on July 6, 2004, about a year before the patent expired. As regards the fundamental Article 83 EPC findings of the Boards, the following claim was important:

19. A transgenic non-human mammalian animal whose germ cells and somatic cells contain an activated oncogene sequence as a result of chromosomal incorporation into the animal genome, or into the genome of an ancestor of said animal, said oncogene optionally being further defined according to any one of claims 3 to 10.

The Examining Division had objected to a broad claim for "transgenic non-human mammalian animals" in a case where "just" a transgenic mouse was disclosed in the description. Even transgenic elephants would be covered. The Technical Board overruled the Examining Division and coined a two-prong test that became timeless:

> 3.2 As the Examining Division pointed out in the contested decision, the claimed invention refers to all non-human mammalian animals, whereas the invention described in the examples has been performed only on mice.
> …
> 3.3 However, the mere fact that a claim is broad is not in itself a ground for considering the application as not complying with the requirement for sufficient disclosure under Article 83 EPC. Only if there are *serious doubts, substantiated by verifiable facts*, may an application be objected to for lack of sufficient disclosure.[1]
> **T 19/90** at sections 3.2 and 3.3 (emphasis added).

A chemical decision that already existed when **T 19/90** was **T 14/83**. Headnotes I and II of this decision read:

> 1. The question whether an invention has been disclosed sufficiently clearly and completely is not to be decided solely on the basis of the content of the claims. If a chemical invention involves the task of manufacturing a product with certain measurable properties (e.g. gel content or degree of polymerisation of a copolymer), and this task is performed by means of a process involving several variables, then the means of its performance are to be regarded as sufficiently disclosed within the meaning of Article 83 EPC if, encountering occasional lack of success notwithstanding strict adherence to the prescribed limits of those variables, clear information, contained in the description, regarding the effects of individual variables on the properties of the product enables the person skilled in the art to bring about the desired properties quickly and reliably in such an event.
> 2. If teaching thus disclosed cannot be defined in a claim precisely enough to rule out occasional failure, such a claim is not to be objected to, provided it is possible to deduce from the description the action to be taken – which also cannot be precisely defined – by way of fine tuning of the variables.

About 14 years later the Board, in a different composition, again pointed out for the **T 19/90** case that the standard for sufficiency is "serious doubts substantiated by verifiable facts": **T 315/03**.

7.1.2.2 **T 694/92** excellently explains the context between the requirements for accepting enabling disclosure and inventive step at the same time. In the opposition, Patentee was confronted with a poster presentation by one of the inventors as prior art for the construction principle captured by the originally granted claims:

> 1. A method for genetically modifying a plant cell, comprising the steps of:
> (a) inserting a plant gene comprising a plant promoter and a plant structural gene into T-DNA, thereby forming a T-DNA/plant gene combination, the plant promoter being adjacent to the 5'-end of the plant structural gene and the plant structural gene being downstream from the plant promoter in the direction of transcription; and
> (b) transferring the T-DNA/plant gene combination into a plant cell, such that expression of the protein encoded by the said plant structural gene is detectable in said plant cell.
> 10. A plant cell produced according to the method of any of Claims 1–9.
> 11. A plant or plant tissue grown from a plant cell according to Claim 10.

1 The Court of Customs and Patent Appeals has held that an enablement rejection is proper if "there is reason to doubt the objective truth of the statements contained [in the specification] which must be relied on for enabling support." **In re Marzocchi**, 439 F.2d 220, 223 (C.C.P.A. 1971).

Patentee argued that there was inventive step because of uncertainties in the presentation but argued at the same time that there was inventive step of the broad claims because of the unexpected expressibility of the phaseolin gene under the control of its own promoter in a dicotyledonous plant. Major research would have been required. Given this situation, the Board was only willing to accept enablement *and* inventive step for the narrow claims of Auxiliary Request III which was limited to Patentee's actual contribution to the art:

1. A method for genetically modifying a dicotyledonous plant cell, comprising the steps of:
   (a) inserting *a plant gene comprising a phaseolin promoter and a phaseolin structural gene* into T-DNA, thereby forming a T-DNA/plant gene combination, the promoter being adjacent to the 5'-end of the structural gene and the structural gene being downstream from the plant promoter in the direction of transcription; and
   (b) transferring the T-DNA/plant gene combination into a dicotyledonous plant cell, such that expression of the protein encoded by said structural gene is detectable in said plant cell.
7. A plant cell produced according to the method of any of claims 1–6.
(emphasis added)

Given Patentee's lines of argument for defending enablement and inventive step, the Board concluded that the experimental evidence and technical details in the description of the contested patent were not sufficient for the skilled person to reliably achieve without undue burden the technical effect of expression in **any** plant cell of **any** plant structural gene under the control of **any** plant promoter and that, consequently, they do not provide sufficient support for a broad claim, such as the above-mentioned granted claim 1. Details of the Board's considerations can be found in the citations set forth in section 7.4.1.2, *infra*.

In its Headnotes **T 694/92** says:

I. Where an invention relates to the actual realisation of a technical effect anticipated at a theoretical level in the prior art, a proper balance must be found between, on the one hand, the actual technical contribution to the state of the art by said invention, and, on the other hand, the terms in which it is claimed, so that, if patent protection is granted, its scope is fair and adequate (see point 3 of the Reasons).

II. In cases where the gist of the claimed invention consists in the achievement of a given technical effect by known techniques in different areas of application and serious doubts exist as to whether this effect can readily be obtained for the whole range of applications claimed, ample technical details and more than one example may be necessary in order to support claims of a broad scope. Accordingly, claims of broad scope are not allowable, if the skilled person, after reading the description, is not able to readily perform the invention over the whole area claimed without undue burden and without needing inventive skill (see points 5 and 19 of the Reasons).

7.1.3 T 301/87 and T 500/91, "Alpha-interferons/BIOGEN"

7.1.3.1 The opposition/appeal case **T 301/87** dealt with a patent which claimed a priority of January 8, 1980. Thus, it was one of the very early cases in the EPO that reflects a pioneering aera in which the first genes were cloned with the goal to recombinantly produce large amounts of proteins known to be useful in therapies. Here, Charles Weissmann did clone cDNAs encoding different types of α-interferons. But the case as such is more relevant for how a reasonable scope of protection can be spanned around a concretely identified nucleic acid sequence. In fact, **T 301/87** is the foundational case that established the "hybridization language" as a means for generalizing a concrete technical contribution in the form of a cloned nucleic acid. It had originally been created in the priority establishing applications of this case by James F. Haley jr.,

a partner at the New York law firm Fish & Neave at the time. The IFN-α case was one of the biggest of its time with co-pending infringement litigations.

Claim 1 of the patent as originally granted read as follows:

A recombinant DNA molecule for use in cloning a DNA sequence in bacteria, yeasts or animal cells, said recombinant DNA molecule comprising a DNA sequence selected from:

(a) the DNA inserts of Z-pBR322(Pst)/HcIF-4c, Z-pBR322(Pst)/HcIF-2h, Z-pBR322(Pst)/HcIF-SN35, Z-pBR322(Pst)/HcIF-SN42 and Z-pKT287(Pst)/HcIF-2h-AH6, said DNA inserts being exemplified, but not limited to, the DNA inserts of the recombinant DNA molecules carried by the microorganisms identified by accession numbers DSM 1699–1703, respectively,
(b) DNA sequences which hybridize to any of the foregoing DNA inserts and which code for a polypeptide of the IFN-α type, and
(c) DNA sequences which are degenerate as a result of the genetic code to the DNA sequences and inserts defined in (a) and (b) and which code for a polypeptide of the IFN-α type.

Looking at this claim, it is important to understand that any DNA sequence covered has to *simultaneously* display *two* features:
– hybridize with a DNA sequence as individualized in claim 1(a); *and*
– encode a polypeptide of the IFN-α type (which, according to the description, meant a polypeptide with either an antiviral activity or the immunological activity of IFN-α).

It is important to note that in such claims, where the definition of the invention relies on the biological activity of a reference protein, it is crucial to properly define that biological activity at least in the accompanying description. Ambiguities can have bad consequences; see **T 923/92**, 7.1.4, *infra*. In any event, suitable functional definitions are acceptable and structural definitions are not necessarily required; see **T 412/06** at section 2.1, and **T 1048/10** at sections 12. to 14. There is not even an obligation to structurally define antibodies in a claim if they can also be clearly defined by functional parameters; see **T 1300/05**.

It is further important to be aware of part (c) of the above claim 1. This part avoids working around the claim by taking advantage of the degeneracy of the genetic code.

The opponents argued that an entire field of research would be blocked if patents with such a scope would be granted and valid.

First, they argued that the claim wasn't clear under Article 84 EPC. However, they had to accept that clarity is not a ground for opposition since the list of grounds for opposition given in Article 100 EPC is exhaustive.

Second, they objected to enablement. In particular, they argued that the hybridization conditions would have to be further defined in the claim, e.g., by adding the term "stringent". The Board disagreed and held:

> Such macromolecular precursors may in appropriate cases be defined as a class by the properties of the end products they relate to and by some structural characteristics, such as similarity based on capability of hybridization with available structures, without necessarily creating uncertainty. In the present case the latter aspect is provided by hybridization with nucleotide sequences made available in microorganisms which contain the basic structures, whilst the IFN-α type antiviral and immunological activity is limiting the class as a functional requirement.
>
> **T 301/87** at section 4.6 (emphasis added).

Furthermore, the Technical Board held:

> Unless claims with such functional connotations are allowable no worthwhile protection is provided against a third party which faithfully repeats the process of the patent and obtains new but equally useful variants of the invention.
>
> Id. at section 4.7.

This position is further explained in section 7.4.2, *infra*.

Nevertheless, when wanting to rely on hybridization language for defining the invention it is advisable to introduce fallback positions into the description, which could read, for instance, as follows:

> The present invention also relates to DNA sequences that hybridize to the above-mentioned DNA sequence and that encode a polypeptide having the biological activity Z. In this context, the term "hybridization" refers to conventional hybridization conditions, preferably to hybridization conditions under which the Tm value is between Tm… to Tm…. Most preferably, the term "hybridization" refers to stringent hybridization conditions.
>
> Important biological activities of the encoded polypeptide are…They can be determined according to… (insert literature).

It seems worthwhile to remember the following remark that the Board made when discussing enablement:

> The requirement for sufficiency is not a matter of satisfying the perfectionist but to enable the skilled person to handle the invention in normal practice.
>
> Id. at section 4.13.

7.1.3.2 Another complex issue of this case was the assessment of inventive step. The first priority-establishing application of the IFN-α patent, "Biogen I", disclosed recombinant DNA molecules containing DNA sequences that encode IFN-α1 and also recombinant DNA molecules for the expression of these DNA sequences. After having filed this first priority-establishing patent application, the Patentee's researchers published said recombinant DNA molecules. Subsequently, the Patentee filed a further priority-establishing patent application, Biogen II, disclosing recombinant DNA molecules containing DNA sequences encoding IFN-α2 (a member of a new class of α-interferons) and a particular recombinant expression vector for the production of IFN-α1.

The Technical Board acknowledged inventive step of the claimed recombinant IFN-α2 DNA molecule and IFN-α1 expression vector IFN-α2 polypeptides displayed an antiviral activity in human cells which was at least 30 times as higher than that of IFN-α1. Furthermore, the level of expression achieved by the novel recombinant IFN-α1 expression vector was 100 times higher than that of the best expression vector disclosed in the intervening publication; see **T 301/87** at section 7.10 et seqq.

The case was remitted to the first instance for further prosecution. The final result was achieved in the second appeal decision, **T 500/91**: the patent was eventually maintained in an amended form.

In the course of **T 500/91** the opponents stated that the claimed α-interferon DNA sequences were obvious over a publication of Taniguchi, in which he described the ±-method and applied it to the isolation of clones said to encode ß-interferon. The Patentee countered that α-interferon, unlike ß-interferon, cannot be superinduced and that, therefore, the ±-method was not suitable for the isolation of DNA sequences encoding α-interferon. The Board accepted Patentee's argument and stated:

> The results communicated in document (15) in relation to interferon-beta were thus not an incentive to try the procedure reported there in an attempt aimed at the production of

> IFN-α. Therefore, in the Board's judgment, a skilled person could not reasonably expect that a procedure, similar to that published in document (15), would, by analogy, be a successful way to obtaining IFN-α by genetic engineering.
>
> **T 500/91** at section 2.3.3.

Furthermore, the opponents stated that the claimed α-interferon sequences were obvious over a publication by Zoon disclosing an N-terminal amino acid sequence of α-interferon. The Board did not accept this line of arguments either and stated:

> In addition and contrary to the Appellants' submission the state of the art at the relevant date (Zoon sequence in connection with documents (109) to (112)) does not describe in detail searching for a particular gene by means of degenerated oligonucleotide probes (mixed probes).
> …
> In respect of the tests performed by Prof. Gassen on behalf of the Appellants in 1990, the situation is similar to that in respect of the tests performed in 1986 in respect of documents [Research Disclosure] (14) and [Taniguchi] (15), i.e. they cannot help to answer the question whether or not the notional person skilled in the art would have expected, at the priority date of the disputed patent, the result which had been proved later to be in fact obtainable.
> …
> The Board therefore concludes that, having regard to the fact that the area of genetic engineering here under consideration was relatively new at the relevant date, having further regard to the uncertainty at that date about facts influencing the success of the attempted recombinant-DNA techniques, and to the absence of a well-established general level of knowledge in this particular technical area, the present successful technical application of recombinant-DNA techniques, according to Claims 1 and 2 under consideration, involves an inventive step.
>
> **T 500/91** at sections 2.3.4 and 2.4

This decision is still a good example of the EPO's approach in the assessment of inventive step of DNA sequences. Important to note is the Technical Board's specific reference to the relevance of the time at which a DNA sequence was cloned in this extremely rapidly developing technical field.

7.1.4 T 412/93, "Erythropoietin/AMGEN"

7.1.4.1 Another big one of the early biotech cases was this one, dealing with the future famous drug erythropoietin which was not originally invented to speed up the Tour de France … Again, there were co-pending infringement litigations. It is important to be aware of this case because it confirmed the acceptability of the "hybridization language" as a generalizing means for nucleic acid claims.

> 1. A DNA sequence for use in securing expression in a procaryotic or eucaryotic host cell of a polypeptide product having at least part of the primary structural confirmation of that of erythropoietin to allow possession of the biological property of causing bone marrow cells to increase production of recticulocytes and red blood cells and to increase hemoglobin synthesis or iron uptake, said DNA sequence selected from the group consisting of:
>   (a) the DNA sequences set out in Tables V and VI or their complementary strands;
>   (b) DNA sequences which hybridize under stringent conditions to the protein coding regions of the DNA sequences defined in (a) or fragments thereof; and
>   (c) DNA sequences which, but for the degeneracy of the genetic code, would hybridize to the DNA sequences defined in (a) and (b).

Again, we note part (c) of the claim which takes care of the tentative "degeneration of the genetic code problem".

An interesting element of the opponents' objections was that because of the absence of any deposit one million hours would have been required to independently clone a human erythropoietin encoding DNA sequence again. This amounted to undue

9 Patenting Antibody Inventions

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Antibodies, it may fairly be said, have been an unprecedented success story. Since it became possible to generate monoclonal antibodies having a predefined target specificity using the hybridoma technology developed by César Milstein and Georges J. F. Köhler in 1975[1], antibodies and antibody constructs/derivatives have revolutionized medicine and biotechnology. These biologics have become indispensable tools in therapy, diagnosis, analytical methods, and as research tools. The number of antibodies among newly approved medicinal products has seen a steady increase over the last decades, and therapeutic antibodies have become ever more prominent in the ranks of blockbuster drugs. Indeed, antibodies and antibody constructs accounted for 5 out of the top 10 pharmaceutical products by worldwide sales in 2020[2] and 2021[3]. It was only due to the SARS-CoV-2 pandemic that the vaccine Comirnaty® replaced the long-term number one best-selling drug Humira® (adalimumab) from the pole position.

9.1 General considerations on antibody patenting in the EPO

It is established case law that antibodies may be defined by structural as well as functional features. In the EPO's "Guidelines for Examination" (GL), a chapter on "antibodies" was introduced for the 2021 edition and further revised in the 2022 version; see GL 2022 II, 5.6. The EPO felt the need to do so to provide for common grounds on general, technical aspects of antibodies and to give guidance on how antibodies may be defined in claims, last but not least in order to fulfill the clarity requirements under Art. 84 EPC and to set the stage for enablement of antibody-related inventions; see GL 2022, G II, 5.6.1. A further focus in the amended "Guidelines" on antibody claims is assessment of antibody claims; see GL 2022, G II, 5.6.2

The review of decisions of the Technical Boards ('the Boards') of the last 5 years and also of decisions discussed in the EPO-book 'Case Law of the Boards of Appeal' (currently 10th edition) evince that a considerable number of (sometimes very valuable) antibody-related patents were revoked or severely limited in scope during appeal proceedings under the Art 123(2)/(3) EPC stipulation, i.e. "impermissible broadening", see e.g. **T 1524/16**, **T 2409/13**, **T 650/18**, **T 509/20**, **T 975/14**, **T 937/15**, **T 304/17**, **T 05/16**, **T 2898/18**, **T 1850/16**, **T 1416/18**, **T 1628/16**, **T 1820/18**, **T 628/15**, **T 2440/13**, **T 1771/19**, **T 3196/19**, **T 2836/19**, **T 776/16** or **T 2842/18.**

T 2842/18[4] is remarkable in as far that, in its assessment of support by the application as filed under Article 123(2) EPC, it applies a "certainty standard" in evaluating the relevance of a literal disclosure of an example that outlines a further clinical trial. We do not think that this is in line with the "direct and unambiguous" gold standard established by **G 2/10**. Such a certainty standard is even more restrictive than what has become known as the "plausibility test" in context with the assessment of inventive

1 Köhler G & Milstein C, Continuous cultures of fused cells secreting antibody of predefined specificity, Nature, 1975, 256(5517): 95–497. César Milstein and Georges J. F. Köhler, together with Niels K. Jerne, were awarded the Nobel Prize in Physiology or Medicine in 1984 for this contribution.

2 Urquart L, Top companies and drugs by sales in 2020, *Nature Reviews Drug Discovery, 2021,* **20**, 253.

3 Urquart L, Top companies and drugs by sales in 2021, *Nature Reviews Drug Discovery, 2022,* **21**, 251. Among the top 10 best-selling drugs by worldwide sales in 2021, the following 5 drugs are antibodies or antibody constructs: Humira® (adalimumab), Keytruda® (pembrolizumab), Stelara® (ustekinumab), Opdivo® (nivolumab) and Trulicity (Dulaglutid, fusionprotein comprising an Fc fragment of human IgG4).

4 Up to completion of this Chapter on March 1, 2023, no pdf of this decision had been made available.

step (Article 56 EPC), industrial applicability (Article 57 EPC) and enablement (Article 83 EPC). Moreover, it is established case law that, unless there are specific circumstances, the assessment of Article 83 EPC requirements is to be kept separate from the assessment of Article 123(2) requirements; see, e.g., **T 2593/11**, Reasons at item 3.4. This decision points out that Article 123(2) EPC aims more particularly at preventing inventors from obtaining protection for inventions they had not thought of at the date of filing and did not put into their application when it was filed, while Article 83 EPC aims more particularly at preventing them from obtaining protection for "theoretical" inventions which could not be carried out at the date of filing. Applying a certainty standard for the assessment of support might lead to situations where inventive step, industrial applicability and enablement can be acknowledged because the relevant disclosure is plausible but where, nevertheless, patentability fails because support has to be denied.

The following overview focuses on aspects in TBA decisions in which clarity (Art. 84 EPC), enablement (Art. 83 EPC), novelty (Art. 54 EPC) and inventive step (Art. 56 EPC) issues of antibody and antibody-related patent claims were addressed by the Boards. Given the volume of relevant decisions in recent years, a thoroughly subjective selection has been made. An attempt is made to discuss recent decisions that illustrate general principles of the case law considering also fundamental, historical decisions.

9.1.1 Allowable claims and formats

The GL 2022, G-II, 5.6.1 provide non-limiting examples of how antibodies or antibody derived constructs/antibody derivates (like antibody fragments, single-chain constructs, mini-or heterobodies, etc.) may be defined in claims. These definitions comprise the *structural definition* via amino acid sequences or encoding nucleic acid sequences, by reference to the (target) antigen, by identification of the bound "epitope" (or target), by reference to a (preferably deposited) hybridoma, by the production process, and/or by reference to further functional and structural features (see, e.g., G-II. 5.6.1.4). Non-limiting examples of *functional definitions* of antibodies (or antibody derived constructs/derivates) in the GL 2022 comprise the recitation of the bound antigen (specificity), but also binding affinity, neutralizing properties, induction of apoptosis, internalization of receptors, and inactivation or activation of receptors, etc. The GL 2022 caution that, if an antibody/antibody derivative is exclusively defined by functional properties, the EPO is to carefully assess "whether the application provides an enabling disclosure across the whole scope claimed" and "whether the functional definition allows the skilled person to clearly determine the limits of the claim"; see GL 2022, G-II, 5.6.1.3. This "careful" assessment by the EPO is also reflected in the case law of the Technical Boards as discussed in this chapter, in particular in context of clarity (Art. 84 EPC), sufficiency of disclosure (Art. 83 EPC), novelty (Art. 54 EPC) and inventive step (Art 56 PC).

9.1.2 Antibody definitions by structural features

In G-II, 5.6.1.1 of the GL 2022 it is emphasized that an antibody, in order to be uniquely defined by its structure only and to have its binding specificity, needs to be defined by the number of Complementary Defining Regions (CDRs) required for its binding. Since three CDRs of each of the variable domains of the light and heavy chains of an IgG are normally responsible for the binding to the antigen/target/epitope, the antibody might have to be defined by this number of CDRs. An example of a claim relating to an antibody with a given specificity and defined by its six CDRs is **T 2127/16** ("Anti-ADDL antibodies/MERCK"; see also claim reproduction in sections 9.5.2.3, *infra*, and discussions in sections 9.1.4, 9.2.2.3 and 9.2.3.2, *infra*, as well as Chapters 5.5.3 or 5.6, *supra*).

If an antibody is defined by less than six CDRs, the corresponding claim may be objected to under Art. 84 EPC (clarity) since the claim might lack an essential technical feature. The requirement of six CDRs may be circumvented if the claim relates to a specific antibody format (e.g., camelid antibodies, nanobodies, etc.), if it is experimentally shown that not all six CDRs are necessary for binding of the antigen/target/epitope and/or if it is made plausible that one or more of the CDRs are irrelevant for the binding.

Often, antibodies are also structurally defined in claims by their full variable regions (i.e. including framework regions), but, where feasible, with a certain flexibility.

For example, in **T 386/08** ("Humanized antibodies that sequester amyloid beta peptide/WASHINGTON UNIVERSITY ST. LOUIS") the claimed humanized anti-Abeta antibody (maintaining desired binding affinities) was defined by its six specific CDRs but also by framework regions that were not concretely identified by sequence but were generically characterized as " 'framework sequence from a humanized immunoglobulin heavy chain'; see also reproduced claim in section 9.3.1.2, *infra*, and section 9.5.2, *infra*, on influence of structural features on inventive step).

A certain flexibility in the framework region was also preserved in the claim as finally maintained in **T 699/19** ("Anti-NGF antibodies/RINAT"; see also section 9.2.5.3 and 9.4.6.2, *infra*) in which the antibody (or antigen binding fragment thereof) was defined via "three CDRs of the heavy chain and of the light chain", said heavy and light chains being defined by their concrete full-length variable regions. The maintained claim in **T 699/19** read:

> An anti-nerve growth factor (NGF) antagonist antibody or antigen binding fragment thereof for use in treating osteoarthritis pain in an individual, wherein the antibody or antigen binding fragment thereof comprises (a) three CDRs from a heavy chain variable region of SEQ ID NO:1; and (b) three CDRs from a light chain variable region of SEQ ID NO:2; wherein the CDRs are Kabat CDRs, Chothia CDRs or a combination of Kabat and Chothia CDRs. (emphasis by underlining added)

In circumstances when an invention is based on the modification of the non-binding part of an antibody, the definition of a constant region may suffice to define an antibody/antibody construct. For example, in **T 784/19** ("Canine immunoglobulins/ZOETI") the Board allowed an antibody definition in a medical use claim by concrete heavy chain constant domain amino acid sequences; see section 9.5.3.4 and 9.5.6.1 (1), *infra*. These sequences related to heavy chain constant domains that comprised specific amino acid substitutions compared to prior art antibodies that led to the (desired) effect that the activation of downstream immune system effector functions was minimized.

9.1.3 Antibodies definitions by functional features

Most common in the EPO are antibody claims that (at least) recited a certain specificity "X" as a functional feature in the formats of "antibody against X", "anti-X antibody" or "antibody specifically binding to target/antigen/epitope X"; see also sections 9.2.2.1 and 9.2.2.2, *infra* on clarity of such claims.

The EPO considers the generation of antibodies against an enablingly provided target/antigen/epitope "X" a matter of routine since the corresponding technology is seen as highly advanced. Therefore, the EPO normally accepts that once a (novel and inventive) antigen and a particular antibody have been provided, it will be a routine matter to identify and/or develop other antibodies having the same specificity; see for example **T 2045/09** ("Anti-ErbB3 antibody/GENENTECH"; Reason in item 21,

and discussion herein see Chapters 3.4, 7.5.1.11, *supra*, and sections 9.2.4.1, 9.2.5.3, 9.3.1.2, 9.3.4.1, 9.3.6.2 or 9.4.2.1, *infra*).

Consequently, also in the case of a newly identified antigen/target/epitope "X", the acknowledgment of novelty and inventive step for "X" means that an antibody to "X" will likewise be considered novel and inventive, even without the disclosure of any actual exemplary antibody.

For instance, in the case underlying decision **T 18/09** ("Neutrokine/HUMAN GENOME SCIENCES")[5] the polypeptide neutrokine-alpha as provided and claimed in the respective patent was considered novel, inventive and industrially applicable. The contested patent also comprised an antibody claim that read:

> An antibody or portion thereof that binds specifically to the Neutrokine-alpha portion of a Neutrokine-alpha polypeptide having the amino acid sequence encoded by the nucleic acid molecule of any one of claims 1(a) through 1(f) or 7 or the Neutrokine-alpha portion of a Neutrokine-alpha polypeptide of claim 15 or 16.

This claim belongs to the broadest class of antibody claims, reciting as functional feature the (here specific) binding to neutrokine-alpha. The invention underlying **T 18/09**, providing for the novel (and inventive) antibody-target "neutrokine-alpha", rendered the antibodies against said target available for the first time.

However, a mere functional definition of antibodies/antibody constructs, etc., by a novel target/antigen that they bind to may have bearings on novelty of the claimed antibody since some prior-art antibodies may have the same (yet implicit) functional property, for example due to cross-reactivities of the prior art antibody. The burden of prove that this is the case is on the party whole raises a corresponding objection or concern.

A given epitope may also serve as functional definition of an antibody. For example, in **T 1964/18** ("Inhibitory anti-NKG2A antibodies/INNATE"; see claim recited in section 9.5.1.2.4, *infra*) the claimed antibody was solely defined by functional features, including the characterization by binding to the same epitope as a given reference antibody.

The mere functional characterization of an antibody, including the definition of its binding to an epitope may, however, not be considered as clear in the sense of Art. 84 EPC when the given epitope is not unambiguously defined. For example, in **T 1911/17** ("BNP (1–32) epitope specific antibodies/BIORAD") the characterization of antibodies by reference to their epitope was not accepted for clarity reasons; see section 9.2.6.2, *infra*, on clarity and section 9.5.4.1, *infra*, on inventive step.

Definition by functional features may, however, by challenging, for example when it is necessary to define the claimed antibodies, antibody constructs or derivatives in addition to the functional definition of the target binding ("specificity to target/antigen/epitope/etc. 'X' ") by additional functional features in order to define the properties of the claimed compounds; see also GL 2022, G-II, 5.6.3 which refer to decisions **T 299/86** ("Monoclonal anti α-IFN antibodies/SECHER" of August 17, 1989, see also Chapters 19.4.4 and 20.5.4, *infra*, and sections 9.2.4.1, 9.2.4.2, 9.2.4.9, 9.3.1 and 9.3.2.4, *infra*) and **T 1300/05** ("RET screening assay/PROGENICS", see also

5 **T 18/09** established that the 'serious doubts substantiated by verifiable facts' requirement originally established for enablement objections in **T 19/90** also applies to the assessment of industrial applicability; see Reasons in items 31 to 33 and Catchword 2 of **T 18/09**, reading: 'An objection of lack of industrial application (Article 57 EPC) requires the same standard of proof as an objection of insufficient disclosure (Article 83 EPC), namely serious doubts substantiated by verifiable facts'.

Chapters 2.3.1 and 7.1.2, *supra*, as well as the detailed discussion in sections 9.2.4.3, 9.3.3.2, 9.3.4.2 or 9.5.1.2, *infra*) as examples.

The discussion of these functionally defined antibody compounds by the Boards tend to focus on clarity and sufficiency aspects. One issue under the discussion is the question whether the application/patent or the prior art provides for tests and assays how a given functional feature can be measured and/or assessed. As reflected in the GL 2022, the EPO also tends to be very strict when it comes to "unusual parameters" in the claims and cautions that "care has to be taken that these do not disguise a lack of novelty". The GL 2022 in G-II, 5.6.3 exhort that in cases when the claimed antibody is exclusively defined by functional features, "it has to be carefully assessed whether the application provides for an enabling disclosure across the whole scope" (which is an Art. 83 EPC question) and whether "the functional definition allows the skilled person to clearly determine the limits of the claim (which tends to be a more clarity related question, i.e. Art. 84 EPC, that is not a ground for opposition).

Early decision **T 299/86** ("Monoclonal anti α-IFN antibodies/SECHER" of August 17, 1989) already dealt such with Art. 84 EPC (clarity) and Art. 83 EPC (enablement) issues of the functional features as reflected in the latest GL 2022. The Examining Division had rejected all claims as not being clear in the sense of Art. 84 EPC and contested, inter alia, the term "specific activity" (of interferon-α as obtained by immunopurification with the claimed anti-α-IFN antibodies) as used in all claims. The Board set this decision of the ED aside and held, for example in Reason in item 4:

> 4. The term "specific activity", used in all the rejected claims is explained in the description of the published application at page 8, lines 33–35. It is stated there that all human interferon titres are quoted in reference research units using the HuIFN-alpha reference research standard 69/19. This means that the activity of human interferon-alpha is measured relative to an international standard reference sample of interferon in Reference Research Units (U) per unit mass (in mg). […] The Board is thus of the opinion that for the skilled person it is clear that the term "specific activity" refers to an international standard and has a clear meaning. Therefore, it is not necessary to incorporate the definition of the feature into the claims, because the meaning of the feature is clearly defined by the description. According to Article 84 the claims shall define the matter for which protection is sought, but they need not give a perfect instruction how the invention is to be used. Moreover, pursuant to Article 84, second sentence, EPC conciseness is a special requirement for claims. One way to draft a concise claim is by making use of features which are clearly defined in the description. There are no objections to such a method, unless the clarity of the claim is so affected that a person skilled in the art would have difficulties understanding what is meant by the claim. No such difficulties arise in the present case.

Further functional features may be seen in antibody/antibody construct or derivatives claims in, e.g., specific affinities, activation or inhibition properties in biological systems, induction of biological processes, etc. Examples of such functional features, besides specificity to a target/antigen/epitope, are provided herein below, e.g., in section 9.2.4.

9.1.4 Antibody definitions by combined structural and functional features

Very commonly in the EPO, antibodies, antibody constructs or derivatives are not only defined by a combination of structural and functional features referring to the target binding ("specificity to target/antigen/epitope/etc. 'X'"), but also by further functional features in order to capture their decisive properties; see also GL 2022, G-II, 5.6.3.

We had discussed in section 9.1.2, *supra*, that the GL 2022 stress that in order to be uniquely defined by its structure only and to have its binding specificity, an antibody need to be defined by the number of Complementary Defining Regions (CDRs) required for its binding. Again, in cases wherein an antibody is defined by less than six CDRs the EPO might raise clarity objections since the claims might lack an essential technical feature; see GL 2022, G-II, 5.6.1.1. The requirement of six CDRs may, however, be circumvented when the application/patent renders it plausible that not all six CDRs are necessary for binding to the corresponding target/antigen and/or when the claims also comprise a (testable) functional feature.

Already **T 387/07** ("Detection of Helicobacter/DAKOCYTOMATION"; see also section 9.3.3.3, *infra*) confirmed that the characterization of an antibody by its CDR(s) can be sufficient; see Reasons at item 14. **T 387/07** concerned an (*in vitro*) detection method in which Helicobacter in stool was to be detected via an antigen-"receptor" complex. The "receptor" was an antibody against H. pylori catalase and the description described monoclonal antibodies that (had not been deposited). However, to be functional, the claimed antibodies needed to also interact with the catalase after intestinal passage. The antibody in this case was more defined by its function as "receptor" than by the CDRs – which were not recited in the claims.

Similarly, **T 418/07** ("Human anti-TNFα antibodies/ABBOTT", see also Chapter 4.2, *supra*, and section 9.3.3.3, *infra*) confirmed the common understanding that the term "antigen binding portions" refers to one and more fragments of an antibody that retain the ability to specifically bind to an antigen. Examples of such binding fragments are the variable domains and the CDRs. The importance of CDR3 motives of the variable light and heavy chain was also recognized by the Board since the CDR3 motives were considered to relate to the epitope recognized; see, e.g., Reasons in items 15.2, and 17.2 to 17.4. This was of importance since the claimed antibody was defined merely by a structural definition of the light chain and the heavy chain CDR3 (and even specific mutations therein). However, this decision also points to the relevance of structural features of a claim but that also the functional ones needed to be considered. Accordingly, in **T 418/07**, the claimed antibodies were structurally defined via just the CDR3 sequences (in claim features "b" and "c") because the claim also comprised a functionally limiting feature, i.e., a defined (dissociation) K_{off} rate from human TNFα (in claim feature "a"). This decision is of particular importance since it confirmed that not all functional (and advantageous) features need to be recited in a claim. In this case the claimed anti- (human) TNF-α antibody had the advantageous features that it was "neutralizing". The Board held in Reasons in item 17.4:

> 17.4 In view of the above considerations the board is satisfied that the independent claims relate to antibodies which are capable of neutralising hTNFalpha and that, although the claims do not explicitly state the neutralisation, this functional feature is to be read into the meaning of the claims by virtue of features
> a) *[defined (dissociation) K_{off} rate],*
> b) *[light chain CDR3 domain definition by sequences and amino acid substitutions]* and
> c) *[heavy chain CDR3 domain definition by sequences and amino acid substitutions)].*
> (underlining, emphasis added; italics, claimed features replaced by concise functional/structural definitions)

Another important decision, not only on antibody definition via combined structural and functional features, is **T 617/07** ("Monoclonal NGF-antagonist antibodies/LAY LINE"; see Chapters 2.3.1 and 6.4.1, *supra*, and in particular sections 9.3.1.2, 9.3.3.3, 9.3.3.4 and 9.3.4.1, *infra*). This decision is of key importance for understanding to what extent claims can generalize the disclosure of a particular antibody (at least in the year 1999). The therein claimed antibodies were defined by structural features (at least

22 Biotech Litigation In Germany And The Netherlands, Perspectives Arising From The Implementation Of The UPC

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22.1 Introduction

Characteristics of Biotech Disputes

Biotech disputes have specific characteristics when compared to pharmaceutical litigation. This already starts with the involved parties. **Originator versus originator** actions are typical. There are usually large and well-funded companies on both sides of the litigation which impacts the litigation strategy. Different to generics which may aim for a quick settlement that will allow them to launch shortly, originators may often not be willing to settle early in the litigation. This is also emphasized by the fact that the market for biologics is more profitable than for small molecules. This means that both sides have an interest in obtaining an injunction or invalidation of the other side's patent. Both sides will push hard in the first round to put more pressure on the other side to get a better position for a settlement. Biotech disputes may also involve originator versus follow-on manufacturer conflicts about **biosimilars**. These biosimilars are highly similar to the reference product notwithstanding minor differences in the active components. Usually, there are no relevant clinical differences between the biological product and the reference product[1].

Another characteristic of biotech disputes is that the analysis of **infringement is complex** and more difficult than for small molecule products. This is due to the involved complex manufacturing processes. Biologics are produced by living cells and biosimilars are not identical. They are only similar due to the use of different cell cultures and different manufacturing conditions. Also manufacturing patents are more important in biotech litigation than in small molecule litigation. Obtaining evidence and proving the case is, therefore, key for biotech litigation.

Moreover, potential infringers often launch at risk because it is difficult to "clear the way" in advance, as there are usually multiple patents covering individual parts of the manufacturing process (just think of the Humira patents' thicket).

Finally, also **regulatory aspects** characterize biotech litigation. Obtaining a market authorization for a biosimilar (a generic version of, e.g., an antibody) is more difficult than for small molecule products and usually requires a heavier investment. The reimbursement schemes by the national health insurers also differ. There is no automatic substitution of the reference product with the biosimilar. This impacts infringement considerations based on the reimbursement schemes.

Harmonization in Europe

There have been a couple of steps to harmonize patent law throughout Europe. The European Patent Convention (EPC) as of 1977 (the first European patent application was registered on 1 June 1978) provides for a central grant of a European patent by the EPO and rules on validity and scope of protection. The **Community Patent Conventions** (CPC) of 1973 and 1989 have never been fully ratified. However, they have been the basis for qualifying acts of infringement in many European countries. The

1 Welch, *Biosimilars 101: An Introduction to biosimilars,* in Gutka, Yang, Kakar, *Biosimilars – Regulatory, Clinical and Biopharmaceutical Development* (Springer, 2018), p. 5 et seq.

Unified Patent Court Agreement (UPCA) also borrows some of its material provisions from the CPC of 1989.

Further effort to harmonize the fragmented patent law has been made by the **European Union** and the Court of Justice of the European Union (CJEU). There are various regulations and directives dealing with patent law and biotechnology such as the "Enforcement Directive"[2], the "Bolar exemption"[3] and the "Biotechnology Directive"[4]. The CJEU has addressed various issues like the requirement of tested validity in preliminary injunction proceedings[5] and liability for wrongfully enforced decisions[6]. Despite all these harmonization efforts, different applications of the provisions in practice remain. This has been reflected in case series litigated throughout Europe like *Pemetrexed*[7]. Nevertheless, these cases also highlight that national courts pay attention to each other and consider arguments of other courts.

The UPC as solution?

The new UPC regime consists of two pillars – the Unified Patent Court (UPC) and the European Patent having unitary effect (EP-UE or **Unitary Patent**). The new Unitary Patent is a pan-European patent which has effect in all Contracting Member States (CMSs). The Unitary Patent can only be litigated before the new UPC. The UPC presents a new procedural system that is specifically designed for patent litigation (and thereby resembles the U.S. Court of Appeals for the Federal Circuit). The UPC is competent not only for the new Unitary Patents but also for classical European patents which have not been opted out from the UPC.

The UPC will provide for a modern set of **rules for procedure** which are adapted specifically for patent litigation. These rules will be a blend of the different systems taking experiences of different countries into account. The main stages of the proceedings will be the written procedure which will resemble the front-loaded German style system in which the written submissions prepare the case. The pleadings will be more comprehensive than those used in litigations, e.g., before UK and US courts. The rules make emphasis to the case management in the form of an interim procedure which is not known in the present German system. The rules also provide for limited discovery and evidence production which also take into account the experience of different countries. The UPC regime is aimed to provide a flexible system which can be adjusted to the need for the case at hand.

The possibility to appoint an **additional technical judge** to the panels of the local and regional divisions which are competent for handling infringement matters shall ensure that there is the same quality for hearing revocation claims before the local and regional divisions as before the central division.

2 Directive 2004/48/EC of the European Parliament and the Council of 29 April 2004 on the enforcement of intellectual property rights.

3 Directive 2004/27/EC of the European Parliament and the Council of 31 March 2004 amending Directive 2001/83/EC on the Community Code relating to medicinal products for human use.

4 Directive 98/44/EC of the European Parliament and the Council of 6 July 1998 on the legal protection of biotechnological inventions.

5 *Phoenix Contact GmbH & Co. KG v HARTING Deutschland GmbH & Co. KG & Ors*, C-44/21 (CJEU 28 April 2022) = GRUR 2022, 811.

6 *Bayer Pharma AG v Richter Gideon et al.*, C-688/17 (CJEU 12 September 2019).

7 Federal Supreme Court, GRUR 2016, 921 – *Pemetrexed;* Federal Supreme Court, GRUR 2016, 921 – *Pemetrexed;* Court of Appeals of the Hague 20 October 2020 – *Pemetrexed; UK Supreme Court 12 July 2017, Eli Lilly v Actavis* UK [2017] UKSC 48; Court of Milan, R.G. 45209/2017 (dated 20 September 2018); Tribunal judiciaire de Paris, 11 September 2020, R.G. No. 17/10421; Stockholm Tingsrätt, PMT-1248/18.

A main factor for the success of this new system will depend on the **quality of the judges**. The UPC has announced the names of 85 judges on 19 October 2022[8]. 61 out of the 85 judges will come from Germany, France, Italy and the Netherlands. Based on the appointed names, there is the basis to see reliable and predictable judgments.

22.2 Overview on Patent Litigation in Germany, the Netherlands and the UPC

The purpose of this chapter is to provide an overview on the status quo of biotech litigation in Germany and the Netherlands and to provide some guidance on how patent litigation may evolve under the UPC regime.

22.2.1 Characteristics of Patent Litigation in Germany

A key factor in German patent litigation is the **bifurcated patent system**. That means that infringement and validity of the patent are heard and decided by different courts. The consequence is that invalidity cannot be raised as defense or counterclaim in infringement proceedings. Defendant can only request a stay of the infringement proceedings pending to the outcome of the validity action. Infringement courts consider a stay only if defendant can show high probability of revocation. Usually, they require that defendant demonstrates invalidity based on prior art which has not been reviewed in prosecution. The main purpose of the bifurcated system is to speed up and simplify infringement proceedings. It is the basis of the German patent litigation system's success but has also led to concerns. The reason is that it allows the plaintiff to obtain an infringement judgment in about one year while revocation proceedings before the German Federal Patent Court or opposition proceedings before the EPO may take about two years. This may then result in an injunction gap, in which plaintiff is able to enforce an injunction and press for a settlement, even though the patent may later be revoked.

The following **main reliefs** against an infringer are generally available in pharmaceutical cases:

(1) **Injunction** against using, offering to sell, sale and importation of the infringing drug, including having goods in possession for any of these purposes. A potential countermove against an injunction is successfully obtaining a compulsory license in separate proceedings.
(2) **Damages** are subject to separate proceedings. The infringement proceedings only declare defendant's obligation to compensate in principle. In separate proceedings (which do not occur often in practice), claimant may choose from three different methods for calculating damages, namely (a) handing over of profits that the infringing party made through infringing sales to the extent these profits are based on using the teaching of the patent. If the patent covers a drug, case law would support claiming a substantial percentage of the profits; (b) reasonable royalty and (c) lost profits suffered by patentee/licensee due to the infringing sales (but hard to prove in practice).
(3) **Information** about the origin and distribution channels of the infringing product, the names and addresses of the manufacturers, suppliers or other previous owners, commercial customers and the quality of the products manufactured or supplied.
(4) **Rendering of accounts** regarding the revenue and expenditures caused by the infringing activities, including a detailed statement of the profit earned.
(5) **Destruction** of infringing products which are in the possession or ownership of the infringer.
(6) **Recall and removal** of infringing products from the distribution channels.

8 A list of names of the judges appointed is published on the UPC's website https://www.unified-patent-court.org/en/news/unified-patent-court-judicial-appointments-and-presidium-elections.

The injunction is more or less automatically granted if infringement is given. It is sufficient to demonstrate an infringing act within or aiming at the territory of Germany. **Permanent injunctions** can be obtained in main proceedings within approximately ten to sixteen months depending on the seized court. **Preliminary injunctions** can be sought as well, usually within two to four months, but require higher hurdles (usually a clear-cut infringement case with readily available evidence and secured validity for which some courts require a favorable decision in the EPO opposition or German nullity proceedings; the burden on affirmed validity of the patent is lower in case a generic pharmaceutical product enters the market shortly before the expiry of the patent).

There are **twelve regional courts** in Germany competent for dealing with patent matters, go-to courts for pharmaceutical cases are Duesseldorf, Munich and – in some distance – Hamburg.

The most common **means of defense** against alleged patent infringement is an opposition to be filed with the EPO or a nullity action to be filed with the Federal Patent Court. Filing the opposition or nullity action as early and quickly as possible enables defendant to achieve a better position in the race for early judgements. Another possible action of defendant in a pharmaceutical case is filing a protective letter which contains the defense arguments. Such protective letters are considered to limit the risk of an *ex parte* preliminary injunction and should in particular be considered after a positive decision of the EPO or the Federal Patent Court on validity of the patent, as the urgency required for preliminary injunctions may revive after such a decision. The protective letter may contain arguments on non-infringement, invalidity and/or lack of urgency.

22.2.2 Patent Litigation in the Netherlands

Unlike Germany, the Netherlands do not have a bifurcated patent system. Infringement and validity are heard by the same court, namely the District Court of the Hague. The District Court of the Hague has exclusive jurisdiction in first instance for Dutch (parts of European) patents (Art. 80 DPA). As a result, both invalidity and infringement can be raised as counterclaims. All proceedings are front-loaded, and the initial briefs should contain a full and complete description of the case.

Regular Proceedings on the Merits

Regular patent proceedings follow the standard procedure laid out in the Dutch Code of Civil Procedure ("DCCP"). Proceedings are initiated by the writ of summons, which contains all relevant details of the dispute (Art. 45(3) DCCP, 111 DCCP). For defendants based in the Netherlands, the notice period (i.e., the first docket date) is at least one week. For defendants abroad, the service period can take up to 3 months. This period differs depending on where the defendant has a known domicile or actual residence (at least 4 weeks if the defendant is from a signatory of the Hague Service Convention; at least 3 months for other foreign defendants (Art. 115 DCCP)). The claimant can set a (substantially) longer term upon preference (Art. 114 DCCP). The writ of summons is first served to the defendant and then registered at the court's registry (Art. 125 DCCP). The defendant is then required to submit its statement of defense (on the first or on a date determined by the judge (Art. 128 DCCP, 136 DCCP). If the defendant wants to file a counterclaim, they must do so together with the statement of defense, otherwise that right is forfeited. The court may, if appropriate, convene a hearing after the receipt of the defendants' response (Art. 131 DCCP). During this hearing, the parties *inter alia* attempt settlement, substantiate their claims and defenses, discuss how the proceedings will proceed and provide the court with any information sought (Art. 87 DCCP). Where no hearing is held, the parties may instead submit additional written pleadings in terms

of Art. 132 DCCP (statement of reply, followed by a rejoinder). After the pleadings are complete, the court will set a date for an oral hearing if it deems fit or if requested by any party. During this, the parties orally present their case and respond to the courts' questions (Art. 87 DCCP). The court then sets a date on which it will give its (final or interim) judgment, usually within six to twelve weeks (Art. 230 DCCP), which term may be extended multiple times.

A patentee who wants to start infringement proceedings based on a national Dutch patent (an NL patent) is obliged to submit a search report on prior art relating to the subject matter of the patent, as published by the Dutch Patent Office ("DPO") or the EPO (Art. 70(2) DPA). The patentee must submit this report along with the other exhibits mentioned in its writ of summons on the first docket date. Similarly, anyone pursuing revocation proceedings based on a national NL patent must submit an advisory report issued by the DPO on the validity of the national patent (Art. 76(1) DPA). This report must be submitted along with the other exhibits mentioned in the writ of summons.

Accelerated Proceedings on the Merits ("VRO")

Most patent cases are tried under the so-called *VRO* regime, an accelerated regime designed specifically for patent cases. In this regime, the court pre-schedules the dates within which pleadings must be filed, and the written submissions are limited to one round. Special procedural rules apply to these proceedings ("**VRO Rules**"). The aim of this regime is to have the case heard within the year and to have a decision within 18 months from the writ of summons. The accelerated VRO regime can be used for both, infringement and revocation actions.

A party wishing to litigate under the VRO regime must first obtain leave of the court (prior to initiating proceedings) and submit its draft writ of summons. If the court allows the request, it will grant leave and provide a fixed schedule for the proceedings. The claimant must then serve the writ of summons and the schedule upon the defendant. The writ has to be served ultimately on the date set in the fixed schedule. On the first docket date, typically four to five months after the date of service, the claimant must enroll the proceedings with the district court and submit all evidence in support of its claim (the exhibits mentioned in the writ and any additional evidence). The defendant must then submit its statement of defense (including any counterclaim) within 10 weeks. If invalidity is alleged (either via counterclaim or as a defense), the claimant must provide its response within eight weeks. Any additional exhibits may be submitted until 6 weeks after the receipt of the claimant's response and any reactive exhibits (in response to the other parties' additional exhibits) may be submitted four weeks prior to the oral hearing.

Four days before the oral hearing each party can file their written pleading notes. The defendant can file a short reply two days later. At the oral hearing the court will ask questions to the parties and the experts. At the end of the hearing each party can make a short oral closing submission and respond to the party's closing submission.

22.2.3 Patent Litigation before the UPC

The UPC will have two instances at which can be litigated: the Court of First Instance and the Court of Appeal in Luxembourg. The latter will be the appellate court, as well as the final court. Like national courts, the UPC can refer questions on the interpretation of EU law to the Court of Justice of the European Union. In the context of Biotech patent litigation, this is specifically relevant for interpretation of provisions in the Biotech Directive (Directive 98/44/EC).

The UPC Court of First Instance is divided into local, regional and central divisions, dispersed over the Member States. Contracting Member States can have a local division or establish a regional division together with other Member States. For example, Sweden, Estonia, Latvia and Lithuania have jointly established a Nordic-Baltic regional division, seated in Stockholm, while the Netherlands has its own local division in the Hague. There will further be four local divisions in Germany (Düsseldorf, Mannheim, Munich and Hamburg) and local divisions in Belgium, France, Italy, Austria, Denmark, Finland, Portugal and Slovenia.

The rules for the language of proceedings differ among the courts. The RoP require litigation at the central division to be in the language of the patent. For local and regional divisions, Member States can choose to have any official language of the EPO and/or their national language as official language of the local or regional division. But parties may also request to litigate in the language of the patent, but this can be denied by the court, after which transfer to the central division is permitted. So, when choosing a forum for litigating at the UPC, one should take into account the language of that court. The Court of Appeal shall have proceedings in the language of the Court of First Instance, so the choice of forum has consequences for any appeal as well. At least the Baltic regional division and the Belgian and Dutch local division have adopted the English language as one of the official languages of the proceedings.

In cases heard by local and regional divisions, there is the possibility of bifurcation, but it is not mandatory like in Germany. When an invalidity counterclaim is brought, the local or regional division may decide how to proceed. Firstly, it can decide to hear both the infringement and the invalidity action itself, just like a national non-bifurcated court would. Secondly, it may opt to bifurcate and refer the invalidity counterclaim to the central division, after which it may choose to stay or simultaneously continue with infringement proceedings. Finally, it can refer both the infringement action and the invalidity counterclaim to the central division.

Like national courts, the UPC offers both provisional and permanent measures.

22.3 Scope of Protection

Even about 45 years after its enactment, **Art. 69 EPC** is still a controversially debated provision of the EPC. It provides the basis to determine the extent of protection of European patents and states that this shall be determined by the claims. Nevertheless, the description and drawings shall be used to interpret the claims. The application of this provision, including the protocol on the interpretation of Art. 69 EPC, has led to different outcomes of claim interpretation of the same European patent throughout Europe, although there has been a clear tendency towards harmonization and alignment of claim construction in recent years. This is particularly true with respect to the Doctrine of Equivalents in the German, Dutch, French and English courts after the *Pemetrexed* decision[9].

9 Federal Supreme Court, GRUR 2016, 921 – *Pemetrexed;* Court of Appeals of the Hague,20 October 2020 – *Pemetrexed; UK Supreme Court,12 July 2017, Eli Lilly v Actavis* UK [2017] UKSC 48; Court of Milan, R.G. 45209/2017 (dated 20 September 2018); Tribunal judiciaire de Paris, 11 September 2020, R.G. No. 17/10421; Stockholm Tinsgrätt, PMT-1248/18.

22.3.1 Determination of the Scope of Protection in Germany

General Principles of Claim Construction

Sec. 14 German Patent Act (GPA) and Art. 69(1) EPC stipulate the **primacy of the patent claims**. The scope of protection is determined by the claims of the patent. They are not only starting points but the basis for construction[10]. Nevertheless, the specification and the drawings shall be used to interpret the patent claims. The claims have to be interpreted by each court independently, even though the principles for claim construction in infringement and nullity proceedings are the same[11]. In view of the bifurcation principle, this also means that infringement and nullity courts may arrive at different claim constructions. With respect to European patents, German courts have to take parallel foreign decisions by courts of EPC member states into consideration[12]. Nevertheless, the claims are to be construed to avoid inconsistencies between claims and specification.

The scope of protection is limited by the claims of the patent, which also means that it cannot extend to those teachings disclosed in the specification but not reflected in the claims[13].

Dependent claims are usually regarded as exemplary embodiments of the invention and, thus, are generally not able to confine the scope of protection of the main claim[14]. Assessing whether dependent claims are admissible for interpreting the main claims depends on whether further aspects have been added to the feature of the main claim in terms of functional improvements. If the dependent claim adds additional features to the respective feature of the main claim, it may not be a basis for interpreting the main claim[15].

The claims are to be construed from the viewpoint of the skilled person. German courts emphasize that the skilled person understands the claim features in a **functional way** and, therefore, they should be interpreted functionally in the context of the technical teaching[16]. The limitation of this functional approach is, however, a spatial, physical, mathematical or chemical term. These terms cannot be reduced to their functions[17].

Prosecution History

The prosecution history can only be used for claim interpretation in very limited scenarios. The **pre-grant prosecution** with statements during examination by patentee or examiner cannot be used as a basis for interpretation. It is only permissible to treat such

10 Federal Supreme Court, GRUR 2004, 1023 – *Bodenseitige Vereinzelungseinrichtung (Bottom separating device)*.
11 Federal Supreme Court, GRUR 2010, 602 – *Gelenkanordnung (Hinge arrangement)*; Federal Supreme Court, GRUR 2004, 47 – *Blasenfreie Gummibahn I (Bubble free rubber sheet I)*.
12 Federal Supreme Court, GRUR 2010, 950 – *Walzenformgebungsmaschine (Roll forming machine)*; Federal Supreme Court, GRUR 2015, 199 – *Sitzplatznummerierungseinrichtung (Seat numbering device)*.
13 Federal Supreme Court, GRUR 2011, 701 – *Okklusionsvorrichtung (Occlusion device)*.
14 Federal Supreme Court, GRUR 2016, 1031 – *Wärmetauscher (Heat exchanger)*.
15 Federal Supreme Court, GRUR 2016, 1031 – *Wärmetauscher (Heat exchanger)*.
16 Federal Supreme Court, GRUR 1999, 909 – *Spannschraube (Clamping screw)*.
17 Federal Supreme Court, GRUR 2016, 921 – *Pemetrexed*.

statements for indications of the understanding of the skilled person and thereby as indications for the correct interpretation[18]. The Federal Supreme Court has left open whether or not the published patent application or previous versions of the patent can be used for claim interpretation[19]. However, earlier versions of the patent can be consulted to find out whether amendments of the claim were executed to distinguish the patent from prior art or just for formal reasons[20]. It is also admissible to rely on the patent as granted as a document for claim interpretation of the patent as amended after opposition[21].

The **post-grant prosecution** history, i.e., statements during opposition or nullity proceedings, are also not admissible sources for claim interpretation. The only exception concerns a scenario where (i) patentee has made a declaration limiting the scope of protection (ii) with respect to a specific embodiment (iii) in the validity proceedings and (iv) this limitation was the reason why the patent was maintained, and (v) the defendant of the infringement proceedings has also been party to the validity proceedings[22]. In this scenario, the defendant of the infringement proceedings can raise a defense based on inadmissible contradictory behavior that the attacked embodiment was not covered by the claim.

Furthermore, the reasons of the parallel opposition and nullity decisions are expert statements which have to be considered by the infringement court, but they are not binding[23] unless the patent has been amended and the specification has not been adapted[24].

Doctrine of Equivalents

The Federal Supreme Court recognizes infringement under the Doctrine of Equivalents. According to its three-step test (the ***Schneidmesser (cutting blade)*** **questions**), an attacked embodiment is equivalently infringing the patent if the modified means have the same effect, are obvious and parity is achieved:

(1) **Same effect:** Do the modified means objectively have the same effect as the means specified in the claim, based on the underlying problem and solution of the patent? It is decisive what effect the patented means has on the solution of the underlying problem. The modified means have to achieve the same effect as the corresponding patented means. In this respect, the Federal Supreme Court has stated that Swiss-type claims are directed to a specific use and not at the manufacture, therefore different effects on the preparation or manufacture are irrelevant and would still fulfill the condition of the same effect[25].

(2) **Obviousness:** Would the skilled person have come up with modified means at the priority date without any particular inventive considerations on the basis of this expert knowledge? The decisive factor here is whether an inventive step would be required to come up with the modified means. In such case, equivalence would be denied[26]. If the modified means have been unknown to the skilled person at the priority date, it is

18 Federal Supreme Court, NJW 1997, 3377 – *Weichvorrichtung II (Softening device II)*, Federal Supreme Court, GRUR 2016, 921 – *Pemetrexed*.
19 Federal Supreme Court, GRUR 2011, 701 (706) – *Okklusionsvorrichtung (Occlusion device)*.
20 Federal Supreme Court, GRUR 2016, 921 – *Pemetrexed.*
21 Higher Regional Court of Duesseldorf, GRUR-RS 2014, 21715 – *Verschleißteil (Wear part)*; Higher Regional Court of Karlsruhe, GRUR-RS 2014, 17797 – *Zugriffskanal (Access channel)*.
22 Federal Supreme Court, NJW 1997, 3377 – *Weichvorrichtung II (Softening device II)*.
23 Federal Supreme Court, GRUR 1998, 895 – *Regenbecken (Stormwater basin)*.
24 Federal Supreme Court, GRUR 2007, 778 – *Ziehmaschinenzugeinheit (Drawing Machine Drawing Unit)*.
25 Federal Supreme Court, GRUR 2016, 921 – *Pemetrexed.*
26 Federal Supreme Court, GRUR 1994, 597 – *Zerlegvorrichtung für Baumstämme (Dismantling device for logs)*.

still possible that the obviousness requirement is fulfilled. In these cases, the assessment depends on whether the general technical progress "just fell into the lap" of the potential infringer[27].

(3) **Alignment with the claims:** Are those considerations conducted by the skilled person in order to arrive at the modification based on the meaning of the teaching of the claims? This is in practice the most important test question. That is, for instance, not the case if the exchange means is the contrary of the teaching of the patent claim, e.g., symmetric and asymmetric. The considerations of the skilled person to use the modified means have to be based on the technical teaching in the patent claims. Parity is denied in case of so-called "selectin inventions". This is the case if the patent description discloses several embodiments and only one embodiment is claimed. Then, the considerations of the skilled person have to be in line with the selection invention at hand[28].

The scope of protection under the Doctrine of Equivalents is limited insofar as the embodiment which equivalently infringes the patent is anticipated or obvious in light of the prior art which is known as a so-called ***Formstein (molding stone)* defense**[29]. With this defense, the defendant is arguing that the specific device is practicing the prior art, and in this scenario the court has to assess whether the specific embodiment is patentable over the prior art. This is the very exception where a German infringement court assesses patentability, but only in view of the specific embodiment. The court cannot make findings in contradiction to the grant of the patent[30].

Claim Construction in Biotech Cases

The scope of an antibody patent claim depends, of course, on the patent drafting. **Broad or limited claims** are possible depending on the underlying basis for validity. Broad claims describe the antibody in a functional manner and may be able to cover a class of antibodies, whereas limited claims may limit the definition of the antibody to specific sequences, which may lead to difficulties in the infringement discussions once an antibody has a slightly different sequence. In such scenarios, the Doctrine of Equivalents may be of limited help because of the specific numerical language in the claims.

The Regional Court of Duesseldorf has dealt in the decision ***Monoclonal antibody***[31] with a couple of claim interpretation issues: (i) In construing the claimed monoclonal antibody, the court found that the patent claim is not limited to an antibody which specifically binds with a certain receptor. Instead, the court found that a binding to receptors fulfilling certain functions is sufficient because the skilled person was aware of these interactions. (ii) The claim required a specific amino acid sequence. The court held that this feature also encompasses deviations of positions which would be regarded by the skilled person as not completely being out of range. The parties did not plead that the deviation of four positions of the antibodies would have led to a completely different molecular structure or to completely different characteristics. In this respect, the court stated that there is no room for applying the case law on specific numerical values which would have supported a limited scope of protection. Instead, according to the court, the claimed sequence is only a synonym for a structural feature. (iii) The court then moved on and determined the degree of fucosylation. In determining the

27 Higher Regional Court of Duesseldorf, GRUR-RS 2016, 21120 – *Partikel-Auffangvorrichtung (Particle catcher)*.

28 Federal Supreme Court, GRUR 2016, 921 – *Pemetrexed*; Federal Supreme Court, GRUR 2012, 45 – *Diglycidverbindung (Diglycid compound)*; Federal Supreme Court, GRUR 2011, 701 – *Okklusionsvorrichtung (Occlusion device)*.

29 Federal Supreme Court, GRUR 1986, 803 – *Formstein (Molding stone)*.

30 Higher Regional Court of Duesseldorf, GRUR-RS 2021, 7737 – *Abstreifeinheit (Scraper unit)*.

31 Regional Court of Duesseldorf, judgment of 20 September 2019, docket no. 4b O 7/18 – *Monoclonaler Antikörper (Monoclonal antibody)*.

right percentage value, the court emphasized the principle that the term has to be construed on its own and a patent may create its own lexica[32].

In ***Antigen binding fragment***[33] the Duesseldorf Court of Appeal dealt with a term for which there was a common understanding of the skilled person (in the case "specificity" and "specific"). The court emphasized the general construction principle that, in a first step, these terms nevertheless have to be construed based on the disclosure of the patent specification. In a second step, the claim interpretation can make use of the meaning pursuant to the common understanding because claims are usually drafted by using terms which have a common meaning in the respective technical field[34].

In the ***anti-HER2 antibody mixture***[35] case the Regional Court of Duesseldorf was presented with the issue of determining, which measurement method has to be applied to demonstrate infringement. The patent was directed to the mixture of an anti-HER2 antibody and one or more acidic variants thereof and claimed that the amount of the acidic variants should be less than about 25 %. Different to a generic scenario where patentee could have relied on the substitution of the originator drug with the generic drug, the patentee needed to demonstrate specific infringement. There was no standardized method of measurement available. The Duesseldorf court found that the percentage of the acidic variants can be determined by any method of measurement available at the priority date. The patent did not refer to a specific measurement method but only mentioned the method according to Bakerbond as an example. In the court's view, the skilled person would have considered the use of several methods for achieving precise results. The applicant provided measurements only based on the Bakerbond method and the court had doubts that these results would clearly and unambiguously demonstrate infringement. The court found that there would have been further methods available at the priority date to determine all acidic variants[36].

In ***Monoclonal mouse antibody***[37], the Duesseldorf Court of Appeal addressed questions of infringement under the Doctrine of Equivalents. The patent claimed a monoclonal mouse antibody binding to a human breast cancer antigen. The attacked product did not contain a monoclonal mouse antibody because the large majority of its amino acid sequences was of human origin. When discussing equivalent infringement, the court found that the skilled person would not have arrived at the exchanged means by following the technical teaching of patent claims. The technical teaching suggested to use antibodies which have been produced by just one species, and the patent only focusses on the species mouse. This would have required the skilled person to modify the antibodies derived from cells of one species so that a majority of the original sequences of an animal would have been replaced by human sequences. Thereby, the skilled person would have left the way outlined by the patent. The court further noted that it has been known in the prior art to replace regions of mouse antibodies with human

32 Regional Court of Duesseldorf, judgment of 20 September 2019, docket no. 4b O 7/18 – *Monoklonaler Antikörper (Monoclonal antibody)*.

33 Higher Regional Court of Duesseldorf, GRUR-RS 2014, 21930 – *Antigenbindendes Fragment (Antigen binding fragment)*.

34 Higher Regional Court of Duesseldorf, GRUR-RS 2014, 21930 – *Antigenbindendes Fragment (Antigen binding fragment)*.

35 Regional Court of Duesseldorf, judgment of 12 July 2018, docket no. 4a O 36/18; BeckRS 2018, 24128 – *Anti-HER2-Antikörper* (*Anti-HER2 antibody mixture)*.

36 Regional Court of Duesseldorf, judgment of 12 July 2018, docket no. 4a O 36/18, BeckRS 2018, 24128 – *Anti-HER2-Antikörper (Anti-HER2 antibody mixture)*.

37 Higher Regional Court of Duesseldorf, judgment of 10 February 2005, docket no. 2 U 80/02, BeckRS 2005, 30350901 – *Monoklonaler Maus-Antikörper* (*Monoclonal mouse antibody)*.

sequences to increase the chances of the therapy. Hence, the skilled person would have expected that the patent specification would contain hints in this direction in case it were to claim protection also for such antibodies with human sequences[38].

22.3.2 Determination of the Scope of Protection in the Netherlands

General Rules of Construction

Art. 69 EPC is enacted in Art. 53(2) DPA and provides the scope of protection: "*The exclusive right is defined by the claims of the patent, the description and drawings serving as an explanation of those claims.*" Following the protocol of Art. 69 EPC, claim construction should result in a fair protection to the patentee with reasonable legal certainty for third parties. The aforementioned balance between a fair protection for the patentee and legal certainty for third parties can influence claim construction to interpret claims beyond their literal interpretation. For the assessment, it is relevant if the skilled person thought there are valid reasons for limitation of the scope of protection[39]. In addition, certain viewpoints may be taken into account, such as the inventive concept behind the wording of the claims, which is also referred to as the "essence of the invention"[40], to avoid an unnecessarily restrictive or extensive literal interpretation[41]. Other factors include the nature of the patent, its contribution to the state of the art[42], and if it is a "pioneer's invention" so that the innovative character of the invention entails that all the possible applications cannot be foreseen by the patentee[43]. Lack of clarity regarding the scope of protection shall operate to the detriment of the patentee and would justify a more restrictive interpretation. The patentee bears the risk of ambiguities in the formulation of a patent[44]. A further consideration is that when variants are disclosed in the description, but not claimed, this can limit the scope of the patent to exclude that disclosed variant[45].

Prosecution History

In the Netherlands, file-wrapper estoppel exists, by which a narrower interpretation of claims can be supported if the patentee has narrowed the scope of the claims throughout the prosecution to get the patent granted. Any publicly available information from the patent prosecution file may be relied upon by an alleged infringer (without restriction) to confirm a defended claim interpretation. However, use of prosecution history by the patentee is only permitted in exceptional circumstances, such as when a skilled person has doubts on the meaning of a claim, even after reading the description and drawings. In practice this hardly ever occurs. This is to ensure that legal certainty for third parties is not undermined. As explained below, prosecution history can also have a role in the (technical) equivalence discussion.

38 Higher Regional Court of Duesseldorf, judgment of 10 February 2005, docket no. 2 U 80/02, BeckRS 2005, 30350901 – *Monoklonaler Maus-Antikörper* (*Monoclonal mouse antibody).*

39 Supreme Court, *AstraZeneca v Resolution Chemicals*, judgement of 8 June 2018.

40 A line of case law which goes back to *Philips/Tasseron*, Supreme Court, judgement of 20 June 1930, although this decision no longer represents good law.

41 Supreme Court, *Medinol v Abbott*, judgement of 4 April 2014.

42 Supreme Court, *AstraZeneca v Resolution Chemicals*, judgement of 8 June 2018; Supreme Court, *Bayer v Sandoz*, judgement of 5 February 2016; Supreme Court, *Medinol v Abbott*, judgement of 4 April 2014.

43 Supreme Court, *AGAv Occlutech*, judgement of 25 May 2012.

44 Supreme Court; *Ciba-Geigy v Ole Optics NJ*, judgement of 13 January 1995.

45 Supreme Court, *Bayer v Sandoz*, judgement of 5 February 2016.

Doctrine of Equivalents

If the allegedly infringing product does not meet all features of the claim, it must be investigated if the differing features are equivalent to the claimed features. In 2020, the Hague Court of Appeal introduced a new equivalence test in the Lilly/Fresenius case about the compound Pemetrexed, in order to align the test of equivalence with Germany, France and the UK[46]. The test comprises a two-step approach. Step one looks at the literal infringement. In this step the courts construe the patent in suit in normal, contextual way as described above, where the claims must be interpreted in the light of the description and the drawings. The second step is then the test of equivalence. The approach as set out by the Court of Appeal has not (yet) been confirmed by the Dutch Supreme Court. However, in several other cases the District Court and the Court of Appeal have applied this two-step approach[47].

For the second step, the assessment whether there is infringement under the Doctrine of Equivalents, the Court of Appeal formulates four requirements that a successful claim of equivalence must meet:

Firstly, there must be technical equivalence. This requirement is met if the product or process with the differing feature solves the same problem as the patent solves and, in that context, the differing feature performs the same function as the claimed feature. This test resembles the function-way-result test that was applicable in the Netherlands before the *Lilly/Fresenius* judgement and is seen in other jurisdictions[48].

Secondly, it must be assessed whether it is appropriate in light of the fair protection for the patentee to take equivalents into account when determining the scope of protection of the patent. In other words, for the person skilled in the art with their common general knowledge (which cannot be taken into account for general claim construction), the patent must disclose a doctrine that may include the application of equivalents.

Thirdly, equivalence must be appropriate in each concrete case so that it leaves a reasonable degree of legal certainty for third parties. The person skilled in the art must understand that the claims leave room for equivalents. Third parties may, in principle, rely on the wording of the claims and lack of clarity is, in principle, to the detriment of the patent proprietor. Recourse to equivalence should nevertheless be possible if, despite the specific wording of the claims, a sufficient degree of legal certainty is ensured, i.e., if the average person skilled in the art understands that the patent claims leave room for equivalents because the doctrine of the patent is clearly broader than the wording of those claims.

In the fourth and final step it needs to be determined that the variant itself is not novel and inventive compared to the prior art. An alleged infringer can defend itself by arguing its product or process is not new or inventive in light of the prior art, in which case it cannot fall under the scope of protection of the patent. This is known as a *Gillette* or *Formstein* defense.

If all four requirements are met, infringement under the Doctrine of Equivalents can be assumed.

46 Court of Appeals of the Hague, judgement of 20 October 2020 – *Pemetrexed.*

47 E.g., Court of Appeals of the Hague, *Pharmathen v Novartis,* judgement of 15 November 2022; District Court of the Hague, *Philips v AB Inbev.,* judgement of 23 December 2022.

48 See e.g., the US Court of Appeals for the Federal Circuit, *Mylan v Aurobindo*, judgement of 19 May 2017.

Claim Construction in Biotech Cases

The scope of protection in relation to biotechnological inventions is provided in Art. 53a DPA and states: "*With regard to a patent for biological material acquired by the invention, the exclusive right extends to any biological material obtained therefrom by propagation or multiplication in the same or differentiated form and having the same properties.*" This is a literal transposition of the Biotech Directive. The scope of this article only extends to products that can be regarded as biological material or a product that consists of genetic information or contains such information[49]. For products that consist of genetic information, the scope of protection should also include other products in which the genetic information is used and the genetic information fulfils its function[50].

In the decision of 20 February 2019[51] the District Court of The Hague rendered a decision on the scope of protection of an antibody patent relating to the active ingredient Trastuzumab. The patent in suit claimed Trastuzumab and one or more acidic variants thereof wherein the amount of the acidic variant(s) was less than about 25 %. The parties were in agreement that in reality the accused product, Herzuma®, contained more than 25 % acidic variants (if all acidic variants that could then currently be identified were counted). As such, this feature relating to the acid variants from claim 1 was not fulfilled literally. However, the patentee argued that this feature of claim 1 should not be interpreted literally, but that the value of 25 % had to be assessed with measurement methods used and available on the priority date. The court ordered that by not specifying the measurement method in the claim, the person skilled in the art would initially understand that what is referred to in the claim is an absolute percentage and the description confirmed this reading. It would have been up to the patentee – insofar as the original application provided basis – to further specify in the claims of the patent which analysis method should be used. In effect, the patentee argued that an acidic variant that could not have been identified with the analysis method described in the patent should not count. Under this theory, the accused product would have had a percentage below 25 % and would therefore infringe. This approach led to considerable legal uncertainty according to the court and the patentee had, during prosecution, it in its power to avoid this uncertainty by specifying the method of measurement in the claim. Therefore, the infringement claim was dismissed.

The court also found that – contrary to the submissions by the patentee – in their claim construction, where all the acidic variants count, no shift in the scope of protection took place over time. A composition that remains under the 25 % level as measured with any method falls under the scope of protection of the claim. A composition that exhibits a percentage of acidic variants higher than 25 % using any suitable method falls outside of the scope of protection. It may happen that methods dating from after the priority date are able to identify new acidic variants, which would allow compounds previously deemed to be infringing to escape, but this does not mean that the scope of protection changes. Such compositions, assuming they remain the same over time, obviously had too high a proportion of acidic variants from the beginning, even if that could not initially have been determined. It could be that in hindsight such a product might have been wrongly taken off the market but that does not mean that those compounds did initially infringe and later not.

49 Supreme Court, *Bio-Chem v Ajinomoto,* judgement of 13 September 2013.
50 CJEU, *Monsanto Technology LLC v Cefetra BV*, judgement of 6 July 2010.
51 District Court of the Hague *Genentech v Mundipharma*, judgement of 20 February 2019 ()- *Trastuzumab.*

22.3.3 Determination of the Scope of Protection before the UPC

The Unitary Patent Regulation states that European Patents with unitary effect shall provide uniform protection and shall have equal effect in all CMSs[52]. Though this states the need for harmonization, it does not provide guidance for determining the scope of protection. The UPCA states that the court shall base its decision on the **EPC and the national law** including case law of the national courts of the CMSs as sources of law[53].

Therefore Art. 69(1) EPC will also under the UPC be the key provision to determine the scope of protection. The CMSs have developed national and somewhat different approaches in determining the scope of protection. Therefore, the task will be on the UPC to develop a **unified approach**[54]. This harmonization process will likely be influenced in the first period by the background of the individual judges on the panels of the UPC until the Court of Appeal has developed guidance to address questions on claim construction. This could also be impacted by the fact that 61 of the 85 UPC judges as appointed on 19 October 2022 come from just four countries, namely Germany, France, Italy and the Netherlands[55]. This may influence forum shopping in the early days of the UPC, e.g., claimant could consider filing an action before a local division whose judges based on their nationality might not be inclined to look into the prosecution history of the patent. The key issues in which the UPC needs to develop a unified approach are the Doctrine of Equivalents and the consideration of the prosecution history.

Doctrine of Equivalents

All CMSs recognize a Doctrine of Equivalents. They treat this as an attack separate from literal infringement. They have developed their own multifactor test[56]. As the *Pemetrexed* cases have shown, the application of these tests may lead to **different outcomes**[57]. The different tests in Germany and the Netherlands have been outlined above. In France, a patent is deemed to be infringed under the Doctrine of Equivalents if different means having the same novel function achieve the same result. In Italy, alternative tests have been developed which seem to be dominated by the function-way-result test, i.e., the question is whether the variant fulfills the same function in the same way and comes to the same result.

The UPC needs to come up with its own approach. It has been argued that the UPC could focus on the concept of the "**inventive idea**"[58]. According to this principle, the skilled person would look behind the wording of the claim and try to determine the essence of the invention and what comes closest to what the invention is in fact. This,

52 Art. 3(2) Regulation (EU) No. 1257/2012 of the European Parliament and of the Council of 17 December 2012 implementing enhanced cooperation in the area of the creation of unitary patent protection.

53 Art. 24(1)(c) and (e) UPCA.

54 Tilmann in Tilmann and Plassmann, *Unified Patent Protection in Europe* (Oxford University Press, 2018), Art. 63 UPCA, margin no. 41 et seqq.

55 A list of names of the judges appointed is published on the UPC's website https://www.unified-patent-court.org/en/news/unified-patent-court-judicial-appointments-and-presidium-elections.

56 Cf. Tilmann in Tilmann and Plassmann, Art. 63 UPCA, margin no. 54 et seqq.

57 Federal Supreme Court, GRUR 2016, 921 – Court of Appeals of the Hague 20 October 2020 – *Pemetrexed; UK Supreme Court 12 July 2017, Eli Lilly v Actavis* UK [2017] UKSC 48; Court of Milan, R.G. 45209/2017 (dated 20 September 2018); Tribunal judiciaire de Paris, 11 September 2020, R.G. No. 17/10421; Stockholm Tinsgrätt, PMT-1248/18. The outcomes also varied in the respective jurisdictions between the different instances.

58 Hoyng, GRUR 2021, 235 (237).