Chicago-Kent Journal of Intellectual Property

Volume 9 | Issue 1 Article 3

4-1-2010

Meanwhile on the Other Side of the Pond: Why Biopharmaceutical Inventions That Were "Obvious to Try" Still Might Be Non-Obvious --Part 1

Timo Minssen

MEANWHILE ON THE OTHER SIDE OF THE POND: WHY BIOPHARMACEUTICAL INVENTIONS THAT WERE "OBVIOUS TO TRY" *STILL* MIGHT BE NON-OBVIOUS – PART I

Timo Minssen*

Abstract:

"In the wake of the seminal U.S. Supreme Court decision in *KSR* the law of non-obviousness has once again become a major topic in patent law. Of crucial importance to the biopharmaceutical industry is in particular the following question: Under what circumstances should an invention that was "obvious to try" be considered obvious in fact? In that regard, a comparative study of the present "inventive step" assessments in Europe is very interesting, since several biotech- and pharma-related EPO decisions, as well as recent high profile judgments of national courts, have not only provided new general guidelines on the European determination of "inventive step" but also addressed specific questions similar to those raised in *KSR* and *In re Kubin*. Considering recent European case law developments, the main goal of this bi-partite article is not to provide yet another detailed analysis of post- KSR developments in the U.S. Instead, the focus is placed on an examination of recent EPO (Part I) and UK case law (Part II) in order to discuss the findings in the context of recent U.S. developments. Special emphasis is placed on DNA-related technology and the "obvious to try" issue. Based on the realization that recent legal and technological developments have made it considerably more difficult for a growing number of therapeutically interesting compounds to meet the non-obviousness standard, this article ultimately argues for a careful elaboration of specifically designed and more flexible exclusivity periods that would be granted after the successful completion of clinical trials. In the absence of sufficient governmental involvement in the development of pharmaceuticals it is hoped that this will assure the further development of obvious and thus unpatentable drugs with a high therapeutic potential."

Table of Contents

Introduction 62
I. The EPO approach 68
A. General principles 68
1. The "problem –and-solution approach" 70
2. The "could – would" approach and the "obvious to try" issue 74
3. The notion of a "reasonable expectation of success" 76
4. Secondary indicia & the (in)significance of structural predictability 79
5. Selection inventions 81
6. The mysterious person skilled in the art & common general knowledge 83
B. Selected DNA and protein- related case law from the EPO 87
1. Basic test: Difficulties in the isolation procedure or in the identification of uses 87
2. Specific case law relating to homologies in different organisms 91
3. Further case law on secondary indicia in biotechnology 94
4. The EPO's position in the Trilateral Projects with special emphasis on gene fragments 97
5. Interim-conclusions 99
C. Article 56 and the quality of evidence in biotechnology: The "plausibility test" 101
1. The first developments towards the current "plausibility test" 102
2. Early concerns 106
3. Recent refinement of the case law 109
4. Discussion: How much is enough? 119
D. Preliminary evaluation 124

*Licentiate of Laws, LL.M., M.I.L., Assistant Professor at the Centre for Information and Innovation Law, Faculty of Law, University of Copenhagen (Denmark). Member of the Epigenetics-research group at the the Pufendorf Institute for Advanced Studies, Lund University (Sweden). This paper did not take into account developments that occurred after February, 16th 2010. The author can be reached at Timo.Minssen@jur.ku.dk.

Summary

Like several other seminal decisions that marked the return of the United States Court of Appeals for the Federal Circuit's (CAFC's) custodial parent to patent law, the 2007 U.S. Supreme Court judgment on the law of "non-obviousness" in *KSR International v. Teleflex* led to vehement reactions. Most notably, the potential implications of the Supreme Courts criticism of an overly rigid application of the TSM-test sent shockwaves through the patent law community. Meanwhile, the United States Patent and Trademark Office (USPTO) and the CAFC, have tried to come to grips with some of the rather unclear statements that are found in KSR, by publishing guidelines and delivering judgments which are the objects of fierce discussions. On the whole, the "non-obviousness" thresholds established by U.S. case law during the previous years have become increasingly problematic for patentees in rapidly evolving high tech areas, such as biotechnological and pharmaceutical companies. Particularly relevant for the biotech-industry is the most recent CAFC decision in *In re Kubin*. In affirming a *KSR* -based obviousness rejection of DNA-related patent claims by the USPTO, the CAFC addressed central issues that are once again the focus of debate, including the doctrine of structural similarity, the qualities and common sense of the "person having ordinary skill in the art" (PHOSITA), predictability, common knowledge, the importance of secondary considerations and the inherent dangers of hindsight, which is related to the central question under which particular circumstances an invention should be held obvious because it was "obvious to try".

While the debate over these complex issues continues, special attention has been drawn to parallel developments in Europe. The European situation is very interesting, since several biotech- and pharma-related decisions of the Technical Board of Appeals at the European Patent Office, as well as recent high profile judgments of national courts, not only provided new general guidelines on the European determination of "inventive step" but also addressed specific questions similar to those raised in *KSR* and *In re Kubin*. Considering recent European case law, the objective of this bi-partite article is *not* to provide yet another detailed analysis of the post-*KSR* U.S. developments. Instead the focus is placed on a detailed examination of recent EPO and UK case law in order to finally discuss the findings in light of the CAFC's decision in *In re Kubin*. More particularly, the article aims to scrutinize specific aspects that are crucial for the biopharmaceutical industry. Special emphasis is put on DNA-related technology and the "obvious to try with a reasonable expectation of success" issue.

In conclusion, it is argued that the *KSR*-induced, more flexible US-approach to obviousness has moved closer to the European approach. In that regard, this article generally welcomes the basic principles that can be derived from *KSR & In re Kubin* for the obviousness examination of DNA-related inventions, indicating the return of the CAFC's reasoning from *In re Deuel* to *In re O' Farrell*. Yet, it is also recognized that specific statements in *KSR* and in *In re Kubin* attracted criticism in both Europe and the US. Moreover, in carefully aligning national case law with EPO precedent, recent decisions by the UK House of Lords and also the German BGH followed a more "patent-friendly" approach with respect to, *inter alia*, the "obvious to try" issue and selection inventions. Referring to those decisions, it is reminded that a fact-based case-by-case assessment of obviousness accepting the general wisdom of the "reasonable expectation of success" and "plausibility" doctrines might in many cases still allow for well-balanced and flexible results. This is particularly true, if due account is taken of further factors, such as the level of competition in the concerned industry, the quality of prior art- suggestions, secondary indicia and the risk of "ex post facto" assessments in the context of rapid high-tech development,. In that regard, recent European decisions provide valuable insights and support for those who fear that KSR inevitably tipped the pendulum towards an overly strict non-obviousness standard, which disregards hindsight problems, the dynamics of the research environment, and the beneficial importance of patents in product development.

Yet, it is also realized that even a more flexible inventive step/non-obviousness assessment cannot, and should not, solve the growing obviousness problems of the biopharmaceutical industry. These problems relate in part to the fact that rapid scientific advances render biological functions ever more predictable. Moreover, it can be expected that novel insights about complex interactions of biological substances will increase the scale and costs of risk assessment in clinical trials necessary for market approval. Patent law, however, does not sufficiently relate to the economic and scientific reality of pharmaceutical R&D. Recognizing the public value of expensive drug development and the therapeutic potential of a growing number of nowadays obvious biopharmaceuticals, this article finally discusses various solutions to assure that such drugs reach the concerned markets. Ultimately, it is argued for a careful enhancement of specifically designed and more flexible exclusivity periods for unpatentable drugs that have successfully completed clinical trials.

- No question is so difficult to answer as that to which the answer is obvious -

George Bernard Shaw 1856-1950

Introduction

Any patent system must find answers to a crucial question that is far more complicated and ambiguous than meets the eye: Which specific features or facts distinguish a patentable invention from a simple improvement or a self-evident combination of state-of-the art technology? Besides being novel, sufficiently disclosed, and useful, any invention must thus be "non-obvious," as required in the United States, or be based on an "inventive step," as required in Europe. More generally, the European inventive-step criteria, similar to the U.S. non-obviousness criteria, require that the invention stands out from the state of the art. This means that, in light of the state of the art, any new invention shall not be obvious to a person skilled in the art.

Following the ideal that patents only are granted for "real" inventions, the non-obviousness/inventive step requirement is supposed to ensure a sufficient qualitative difference between the claimed invention and the state of the art. While the novelty examination aims to guarantee that there is a quantitative difference between the invention and the state of the art, the inventive step/non-obviousness assessment basically attempts to determine whether a development can be regarded as a sufficient technical advance to justify the award of a patent. In theory, such a result promotes the development of technology by providing economic incentives for inventors to focus on truly new and innovative products in often uncertain scientific areas, while avoiding economical reward for the production of insignificant improvements or trivial changes to the prior art.[1] Thus, the non-obviousness/inventive step requirement may also be accurately described as a "non-triviality" requirement,[2] which in combination with the other patentability requirements protects the public domain from unjustified claims of exclusivity.[3]

The practical and commercial impact of this requirement on both patent litigation and prosecution can hardly be underestimated, because it allows patent offices and courts to deny or invalidate a patent even where it claims a useful product or process that has never been previously realized. This, and the fact that the other basic patentability criteria have traditionally been interpreted rather mildly,[4] explains why many patent lawyers consider the

---

[1] *See* Edmund Kitch, *Graham v. John Deere: New Standards for Patents*, 1966 SUP.CT.REV. 293, 301 (1966) (suggesting that § 103 should reward patent for those innovations that would not have been developed without patents); *see also* Katsuya Saito & Rosemary Sweeney, *Assessment of Inventive Step or Obviousness in the United States, Europe and Japan*, Student Research Papers, School of Law, University of Washington (2002), p. 1, *available at* http://www.law.washington.edu/casrip/harmonization/PDF/obviousness.pdf (last visit: 11 May 2007), (referring to Fritz Machlup, *An economic review of the patent system, A Study of the Subcomm. on Patents, Trademarks, and Copyrights of the Senate Comm. on the Judiciary*, Study No. 15, 85th Cong., 2d Sess. (GPO, 1958)).

[2] *See* Robert Merges & John Duffy, *Patent law & Policy*, 612 (4th ed., LexisNexis 2007).

[3] Craig Allen Nard & R. Polk Wagner, *Patent Law*, 102 (Foundation Press 2008) (referring to the US Supreme Court decision in *Bonito Boats, Inc. V. Thunder Craft Boats, Inc.*, 489 U.S. 141, 156 (1989), where the Supreme Court underlined that the novelty and non-obviousness requirements "are grounded in the notion that concepts within the public grasp, or those so obvious that they readily could be, are the tools of creation available to all").

[4] Yet, it should be noted that recent developments concerning the "industrial application/utility" and "sufficient disclosure" standards now require in both Europe and the US a more careful preparation of patent applications, which must be based on plausible and coherent data and thus should not be handed in too early, *see* e.g. Michael Hopkins *et al., DNA patenting: the end of an era?*, 25 NATURE BIOTECHNOLOGY 185, 187 (2007). *See also* Timo Minssen, *När anses en bioteknologisk uppfinning vara komplett och praktisk användbar*- Del I -USA, NIR 201-60 (2008), & Del II - Europe, NIR, 339-87 (2008) (in Swedish). Concerning the novelty-inventive step relationship *cf.* Sir Hugh Laddie, *Patents – what's invention got to do with it*, in: Vaver & Bentley (ed.), Intellectual Property in the New Millenium 92-93 (Cambridge Univ. Press 2004) (explaining that although the

"inventive step/non-obviousness" prerequisite to be the most important of the basic patent criteria and call it the "final gate-keeper"[5] or "holy grail"[6] of patent law.

However, the importance of this requirement is matched by the complexity of its assessment, because it attempts to measure *technical accomplishment* – a quality even more abstract and unpredictable than novelty, utility/industrial application or sufficient disclosure. Although the "inventive step/non-obviousness"determination is ultimately a question of law, any decision usually depends on a highly fact-based inquiry also referred to as a "jury question ". One consequence of the factual nature of the inquiry is that precedents must be treated cautiously, and this includes even those precedents that involve decisions on the same invention.[7] The evaluative nature of the inquiry also implies that reasonable people, including judges, juries, patent examiners, or even the rather mystical imaginary persons skilled in the art, can easily reach different conclusions at different times, thus making it extremely difficult to foretell the result of an obviousness attack or objection.[8] This unpredictability has led to the arbitrary use of discretion and to accusations of uncertainty. One consequence of these inherent and perhaps inevitable problems is that, on appeal, courts have often been rather cautious to overturn decisions of the lower courts,[9] as indicated by the following statement from the UK House of Lords:

---

law of anticipation is a rigid test, it is of little commercial importance as ground of invalidity, since anticipations who do not also give rise to strong arguments of obviousness, are rare and normally easy to circumvent).

[5] *See* Merges & Duffy, *supra* note 2, at 612.

[6] *See* J. Sai Deepak, *The elusive quest for the definition of obviousness – Patent Law's Holy Grail*, 1, Winner of the 2008 ATRIP Essay Competition, *available at* http://www.atrip.org/26.htm (last visit: February 4th, 2009).

[7] Lionel Bentley & Brad Sherman, *Intellectual Property Law*, 489 (3rd ed., Oxford University Press 2009), (adding: "though juries have not sat in patent cases in the *UK* since 1883"). Note, however, that the "non-obviousness" assessment is still jury question in the US where the CAFC decision in *Rentrop v. Spectranetics Corp.*, 550 F.3d 1112, 89 U.S.P.Q.2d 1417 (Fed. Circ., Dec. 18th 2008) has recently confirmed pre-KSR "non-obviousness" jury-guidelines. Particularly interesting was how the CAFC addressed the defendant's argument that the statement in the jury instruction "the test for obviousness is not whether or not it would have been obvious to try to make the invention" would violate KSR, where the Supreme Court had held that the CAFC was in error to hold that a "patent claim cannot be proved obvious merely by showing that the combination of elements was obvious to try." The CAFC managed to logically combine these two statements, noting that the jury instruction "does not imply that a showing that the specific combination of elements was obvious to try is insufficient to find obviousness." Note further that in November 2009 the Supreme Court rejected Medela's petition for a writ of certiorari 2009 in *Medela AG and Medela, Inc.,v. Kinetic Concepts, Inc., KCI Licensing, Inc., KCI USA, Inc., and Wake Forest University Health Sciences, No. 09-198* arguing that the conclusion of obviousness should be made by a judge rather than a law jury (Cert. petition filed on August 11, 2009, 2009 WL 2509227; conference of: November 13, 2009. Petition denied). On December, 11th 2009 the Supreme Court was once again confronted with this question in a similar petition for certiorari, *see Acushnet Co. v. Callaway Golf Co., Supreme Court No. 09-702,* following *Callaway Golf Co. v. Acushnet Co., 576 F.3d 1331* (Fed. Cir. 2009) (Dyk, J.). In essence Acushnet asked the Supreme Court to hold that a court reviewing a jury's (obviousness) verdicts must always independently render its own legal conclusion regardless of whether one or all of the jury's underlying findings are accepted as adequately supported by the evidence. Consequently, it was further argued that a jury's verdict on obviousness should be seen as entirely advisory as to the ultimate legal conclusion. On February 22nd 2010, the Supreme Court denied the petition.

[8] William Cornish, *The Essential Criteria for Patentability*, 14 IIC 765, 771 (1983) (pointing out that this "contributes significantly both to the insecure commercial value of many patents and to the cost of litigating their validity."); Regarding the effect of the post grant opposition procedure at the EPO on the threshold of inventive step *see* a recent paper by Catarina Holtz, *Opposition only after Grant- Any Effects on Inventive Step at the EPO?,* GRUR Int., Heft 8-9 (2008), 653 – 657 (concluding after having conducted a limited study of recent EPO case law that no indications were found that were strong enough to support the supposition that the level of inventive step has declined as a result of the post-grant opposition procedure. Nevertheless she underlined that more profound and detailed is needed and that this topic must be discussed further).

[9] *See* Bentley & Sherman, *supra* note 7, at 489. *See also* Gregory Mandel, *Another Missed Opportunity: The Supreme Court's Failure to Define Non-Obvious or Combat Hindsight Bias in KSR v. Teleflex*, 12 LEWIS & CLARK L. REV. 323, 342 (2008).

> *The need for appellate caution in reversing the judge's evaluation of the facts is based upon much more solid grounds than professional courtesy. It is because specific findings of fact, even by the most meticulous judge, are inherently an incomplete statement of the impression which was made upon him by the primary evidence. His expressed findings are always surrounded by a penumbra of imprecision as to emphasis, relative weight, minor qualification and nuance (as Renan said, la vérité est dans la nuance), of which time and language do not permit exact expression, but which may play an important part in the judge's overall evaluation. It would in my view be wrong to ...[authorize or require]... an appellate court to undertake a de novo evaluation of the facts in all cases in which no question of the credibility of witnesses is involved. When the application of a legal standard such as negligence or obviousness involves no question of principle but is simply a matter of degree, an appellate court should be very cautious in differing from the judge's evaluation.*[10]

The complexity of the non-obviousness assessment has for long time also been recognized by U.S. judges, who have described the requirement *"as fugitive, impalpable, wayward and vague a phantom as exists in the whole paraphernalia of legal concepts."*[11]

Regardless of these inherent problems, in both Europe and the United States, the law of inventive step/non-obviousness applies with equal force to inventions from the pharmaceutical and biotechnological arts as it does to inventions from other disciplines. In that context, the complex, often unpredictable, nature of these arts and the rapid increase of novel insights on the complexity and interrelation of the involved mechanisms lend additional problems to the already intricate inventive step/nonobviousness analysis. At the same time, however, one should also note that most of the initial problems, which scientists faced during the 80's and 90's, are now solved. For example, due to the developments in computer technology, the identification and preparation of DNA sequences is now by and large a routine process. Moreover, while many problems still remain, the specific functions of DNA and protein sequences are slowly becoming ever more predictable.

Even from a more general perspective, the spectacular growth of the capacity of high-tech research during the last forty years cannot be ignored. Particularly, great resources are committed to research in pharmaceuticals and biotechnology, because the promises of the technology and the potential rewards in global markets are so great. Thus, unsurprisingly the competition between "originator" pharmaceutical companies and "generic" companies is becoming an increasingly important feature of the global pharmaceutical market. As a consequence, competition is extremely fierce. In this climate the judicial interpretation of the inventive step/non-obviousness requirement tends to take on a life of its own as an important weapon in the armory of those challenging the validity of a patent.[12] In this particular multi-faceted environment, the more specific requirements for the inventive step condition must be continuously reconsidered, and this is specifically true with respect to biopharmaceutical inventions and genetics.[13] Yet, the various thresholds established for this requirement are

---

[10] Lord Hoffmann in *Biogen v Medeva* (1997) RPC 1 at p. 45.

[11] Judge Learned Hand in *Harries v. Air King Products*, 183 F.2d 158, 162 (2d. Cir. 1950).

[12] Lord Walker in *Conor Medsystems Inc. v Angiotech Pharmaceuticals Inc.* (2008) UKHL 49, at para 47.

[13] Steven Crespi, *Biotechnology Patenting: The Wicked Animal Must Defend Itself*, EIPR, 431 ff. (1995); *cf.* Aditi Mathur & Kshitij Dua, *A Comparative Study of DNA Sequence Patenting in the USA, Europe & Japan, and Suggestions for the Course of Action for India*, 12 CASRIP Newsletter 2 (Fall 2005), fn. 8, *available at* http://www.law.washington.edu/Casrip/Newsletter/default.aspx?year=2005&article=newsv12i2MathurDua (last visit 10 July 2009) (pointing out that, "[B]iotechnology was considered a field that is highly unpredictable, on par with the field of chemistry, because of which, it could have provided a framework in which non-obviousness would be more readily acknowledged. However, recent advances in biotechnology and computer technology have changed this situation. Due to ongoing progress in computer technology, advances in algorithms and the accumulating body of experiments and results, fields such as hybridoma technology, combinatorial chemistry, drug design with computers, EST sequencing, and SNP genotyping are steadily becoming more predictable. Maintaining the current standard for non-obviousness in an environment in which unpredictability is steadily decreasing may lead to cases in which non-obviousness must be denied.").

becoming increasingly problematic for patentees and other stakeholders in these rapidly evolving high tech areas.

In that context, one crucial issue relates to the key question: under what circumstances should a biopharmaceutical invention resulting from a combination of prior art features, and where that combination was "obvious to try," be denied patent protection for lack of inventive step or non-obviousness? Evidently, whenever complex technologies are concerned, such situations entail a great risk of arriving with hindsight knowledge at a wrongful obviousness conclusion. Although working with or combining previously known compounds, processes or methods within a new field of application may be considered "obvious to try," numerous difficulties may still be involved in the process. Moreover, the chosen paths that later prove to be successful might have previously been considered by the majority of scientists to be the least attractive or most improbable route to success. Addressing this problem, the EPO therefore finds a technical solution obvious only if it would have been obvious to combine - or try to combine - the documents representing the previous state of the art *and* if the combination of the features would be expectedly successful and lead to previously expected results. This test is called the "obvious to try with a reasonable expectation of success" test. It is regularly applied by the EPO wherever the inventor at the priority date has a number of known technical options that might, in hindsight, be tried in order to arrive at the claimed invention.

The "obvious to try with a reasonable expectation of success" test is also recognized and discussed in the U.S. patent system. At least initially, it was readily applied by the CAFC under the well known Teaching-Suggestion-Motivation (TSM) test in a series of DNA related cases.[14] As it turned out, however, in the following years the early CAFC approach was not applied consistently. Whenever the obviousness of product claims on isolated DNA sequences had to be determined, U.S. courts began to focus on a different approach for determining *prima facie* obviousness. That approach was predominantly based on chemical-compound-based logic, including the "structural similarity" and "selection invention" doctrines.[15] While this shift in approach led to acceptable results in the first cases,[16] the outcome of the CAFC's 1995 decision in *In re Deuel* was much more debated.[17] Here, the

[14] *See In re O'Farrell*, 853 F.2d 894, 904 (Fed. Cir. 1988) (where it was held that in the view of the prior art there was a "reasonable expectation of success", and, in particular, that obviousness does not require absolute predictability of success.) For a different result under the same principles, *see In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). A more comprehensive discussion of these cases is provided by Timo Minssen, *Patenting Human DNA Sequences in Europe and the US*, Licentiate thesis, Lund University, 112 ff. (2005). *See also* Judge Rich's 1963 opinion in *In re Papesch*, 315 F.2d 381, 391 (C.C.P.A. 1963) (admonishing the USPTO to look beyond structure when analyzing the obviousness of a new chemical, directing attention to how the chemical works, rather than merely what it looks like.).

[15] For a detailed explanation of the mentioned doctrines, see Anita Varma & David Abraham, *DNA is Different* 9 HARV. J. L. & TECH. 53 ff. (1996).

[16] *See* e.g. *Amgen Inc. v. Chugai Pharmaceuticals Co.*, 927 F.2d 1200, 1213 (Fed. Circ. (1991) (finding that DNA is a chemical compound - albeit a complex one); and *In re Bell*, 991 F.2d 781, 784 (Fed. Cir. 1993) (where the previously disclosed amino acid had an extremely high redundancy resulting in myriads of possible coding DNA sequences and an arguably rather low expectation of success. Here, the Court did not yet completely dismiss the relevance of known cloning methods to the obviousness of the gene. Instead, the Court underlined that the prior art "taught away" from the claimed invention. However, the explicit consideration of cloning methods left at least a slight chance that the Court might in the future find claims to DNA sequences obvious when the protein sequence was known (i.e. when the cloning methods would have become routine and would lead to a "reasonable expectation of success"). Yet, this possibility was foreclosed two years later by *In re Deuel*, *see infra* note 17).

[17] *In re Deuel*, 51 F.3d 1552 (Fed. Circ. 1995). Even though *Amgen, Bell* and *Deuel* have to be distinguished from the decisions in *O' Farrell* and *Vaeck*, which were primarily concerned with process claims, literature has been predominantly critical of *Deuel*, arguing *inter alia* that the CAFC has failed to adjust existing paradigms for obviousness to the "dual nature" of DNA related technology, cf. part II.

court, or more specifically Judge Lourie, applied an extremely formalistic approach, simply stating that "obvious to try" was not the standard for determining obviousness. Thus, the CAFC decided not to focus on the "reasonable expectation of success" concept. Prior disclosure of a structurally different amino acid sequence did not render the DNA sequence *prima facie* obvious due to the degeneracy of the genetic code. Prior art methods for isolating and sequencing some undefined DNA were held to be essentially irrelevant, since such methods did not define the claimed sequence with the precision necessary to render it obvious over the protein it encoded.[18] Thereby the CAFC focused on the obviousness of the DNA sequence itself rather than on the obviousness of the method for isolating it. The court held that the DNA molecule was nonobvious and patentable because the structure of its sequence could not be predicted without prior disclosure of sufficiently similar DNA molecules. The legal effect of this decision was that DNA molecules could be held *prima facie* nonobvious, although a PHOSITA would, in light of the prior art, consider it "obvious to try" to obtain the DNA molecule utilizing prior art amino acid sequences. In that regard it did neither matter that familiar prior art methods would (arguably) entail a "reasonable expectation of success" to arrive at the claimed DNA by following a routine procedure. Thus, it can be argued that the CAFC's decision in *In re Deuel* represents the "high watermark" of a very formalistic application of the TSM test for DNA-related inventions which significantly lowered the obviousness bar for claims on DNA.

Yet, as of April 2007 the U.S. Supreme Court decision in *KSR v. Teleflex* considerably changed the U.S. law of nonobviousness once again.[19] In *KSR*, the Supreme Court essentially upheld the TSM standard, but criticized the Federal Circuit's rigid application of the TSM test "to the exclusion of common sense" by requiring explicit suggestion, teaching or motivations in the prior art. More specifically, the Supreme Court held that (1) the Court and Patent Examiners should not be limited to considering only the specific problem the patentee was trying to solve; (2) a person skilled in the art in attempting to solve the problem should be regarded to be a person with "ordinary creativity" and that "common sense" teaches that he should not be restricted to consider only those prior art elements designed to solve the same problem[20]; and (3) a combination determined to be "obvious to try with a reasonable expectation of success" might very well be regarded to be a reasonable indicator that the combination was *in fact* obvious, contrary to some of the more extreme "structural predictability" related findings of the CAFC in *In re Deuel* .

Meanwhile, by publishing guidelines and delivering decisions that are the object of fierce discussions, both the USPTO and the CAFC have tried to come to grips with some of the rather unclear statements found in KSR.[21] Although several judgments indicate that there

---

[18] *Id.* at 1559 (The Court added that the outcome might have been different, if there had been a lack of redundancy. Yet, it should be noted that the CAFC required an extremely high degree of predictability for the conclusion of obviousness. In a case where a previously disclosed protein lacked redundancy it would arguably have been self evident to arrive at the claimed DNA). *See also* Amy Nelson, *Obviousness or Inventive Step as Applied to Nucleic Acid Molecules: A Global Perspective* 6 note N.C. J.L. & TECH. 1, 6-8 (2004) (demonstrating further how the PTO still found facts that could be distinguished from *Bell* and *Deuel* in order to establish obviousness and referring *inter alia* to *ex parte Movva*, 31 U.S.P.Q.2d 1027 (1993), and *ex parte Goldgaber* 41 U.S.P.Q.2d 1172 (1995).).

[19] *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398 (2007), 82 U.S.P.Q.2d 1385 ("KSR").

[20] *Id.*, 82 U.S.P.Q 2d 1385, 1397 ("a person of ordinary skill in the art is also a person of *ordinary creativity*, not an automation." & "*common sense* teaches...that familiar items may have obvious uses beyond their primary purposes, and in many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle.").

[21] For a more detailed analysis of KSR *see* Timo Minssen, *The US Examination of Nonobviousness After KSR v. Teleflex with Special Emphasis on DNA-Related Inventions*, 39 IIC 8, 886-917 (2008) (It should be noted that the Supreme Court in KSR had never explicitly overruled *In re Deuel*. Rather it questioned some of the CAFC's findings. Yet, it will be demonstrated below, the CAFC had now more explicitly repudiated *In re Deuel.*).

is still considerable leeway for arguments in favor of the non-obviousness of biopharmaceutical inventions,[22] it seems on the whole that the "non-obviousness" threshold established by U.S. case law during the last years has become an ever more difficult hurdle for biopharmaceutical inventions.[23] As it will be discussed in more detail in part II this is especially true for DNA-related technology.

Particularly relevant for the biopharmaceutical industry is the most recent CAFC decision in *In re Kubin*.[24] In affirming a KSR-based obviousness rejection of DNA-related patent claims by the USPTO and by repudiating the previously controlling rigid *In re Deuel*- "structural predictability" doctrine, the CAFC focused explicitly on the "obvious to try with a reasonable expectation of success" issue and specified how this question should be addressed in the biotechnological area. The Federal Circuit's *Kubin* decision raises the legitimate issue of what will not be obvious in biotechnology under the *In re Kubin* "obvious to try" doctrine. Many patent experts assume that *KSR* and *In re Kubin* represent overdue and necessary steps in the right direction of preventing patent thickets of numerous trivial patents and establishing a higher quality of patents with a proper scope of protection that corresponds to the inventor's actual contribution to the state of the art. In contrast, others fear that KSR inevitably tips the pendulum towards an overly strict non-obviousness standard that disregards hindsight problems, the dynamics of the research environment, and the importance of patents in beneficial product development.

As the U.S. debate over these multi-faceted issues continues, particular attention is drawn to parallel developments in Europe. The situation in Europe is very interesting indeed, since several biotech- and pharma- related decisions of the Technical Board of Appeals (the Board) at the European Patent Office (EPO), not only provide new general guidelines on the European determination of "inventive step," but also address specific questions similar to those raised in *KSR* and *In re Kubin*. The same is true for recent high-profile judgments of national courts that followed a more patent-friendly interpretation of the "obvious to try" and selection invention issues.

Recognizing that a comprehensive evaluation of the complex and case specific "inventive step" assessment falls outside the scope of the analysis, this bi-partite article provides a technology-specific evaluation of some key findings derived from European developments in order to finally discuss these findings in the light of *KSR* and *In re Kubin*.

---

[22] Rebecca Eisenberg, *Pharma's Nonobviousness Problem*, 12 LEWIS & CLARK L. REV. 375, 380 (2008) (highlighting that the Federal Circuit had even before KSR applied a rather flexible obvious assessment in the pharmaceutical arts. Yet, she also recognizes that as for DNA-related patents the situation has changed considerably after *KSR*.); *see also* Andrew Trask, *"Obvious to Try": A Proper Patentability Standard in the Pharmaceutical Arts?*, 76 FORDHAM L. REV. 2625 - 2668 (2009) (reviewing the history of the "obvious to try" test and considering the CAFC's post-KSR inconsistency regarding obviousness in the pharmaceutical arts. In the end it is argued that KSR does not permit courts to deny the patentability of a pharmaceutical invention simply because it would have been obvious to try).

[23] *See* Timo Minssen, *supra* note 21, at 886. As for empirical evidence *see also* the recent study conducted by Dennis Crouch, *Understanding the role of the BPAI: Ex parte rejection rates on appeal*, University of Missouri School of Law Legal Studies Research Paper No. 2009-16 (2009) (concluding that, by far, the most common issue on appeal at the USPTO is obviousness and that 87% - 90% of cases decide an obviousness- issue. According to the author only 18% of BPAI decisions involving patent-claims in biotechnology and organic chemistry focus on issues other than obviousness and novelty. The situation is even more extreme in other technological areas where only 4% of appeals consider neither obviousness nor novelty. Comparing results by issue, the author also found that obviousness rejections are more likely to be affirmed than are other types of rejections. Cases that discuss neither obviousness nor novelty are reversed in 74% of cases. Finally, it is concluded that the BPAI is generally considered to play an ever more important role due to a dramatic rise in the number of appeals being filed, as it has been underlined by all recent patent reform legislative proposals.).

[24] *In re Kubin*, 561 F.3d 1351 (Fed. Cir. 2009).

The focus is laid on aspects that are of central importance for the biopharmaceutical industry with a special emphasis on DNA-related technology.

Accordingly, Part I first analyzes the EPO approach to the examination of inventive step in biotechnology. Particular weight is placed on the "obvious to try with a reasonable expectation of success" issue and DNA-related inventions. Moreover, the recent developments towards the so-called "plausibility test" will be analyzed and discussed. Part II subsequently analyzes recent case law developments in the UK that particularly relate to the "obvious to try" issue.[25] Next, the results of the previous analysis are summarized and compared within the European context, including short references to interesting parallel developments in Germany. This provides the basis for a discussion of the findings in light of the current U.S. debate on *KSR* and in particular *In re Kubin*. One central question that will have to be dealt with is: How can we ensure the further development of a growing number of old or obvious and thus unpatentable drugs with a high therapeutic potential? In order to address this crucial problem several *de lege ferenda* options will be considered including a reform proposal that argues for a careful enhancement of specifically designed and more flexible market exclusivity periods for unpatentable drugs that have successfully completed clinical trials. Finally, this article concludes with some general remarks.

I. The EPO approach

To illustrate the EPO's approach in the inventive step assessment of biopharmaceutical, and in particular DNA- related inventions, Section A begins with a description of some general principles that provide the basis for an inventive-step analysis. While it is inevitable that this general description already refers to DNA-related case law, Section B then describes in more detail how the EPO actually applies the identified principles in specifically selected DNA-related case law. Section C continues with a summary of more recent biotech-related case law from the EPO in which the so called "plausibility test" was first developed and subsequently refined. After an evaluation of the consequences of these new developments for patent applicants in the biopharmaceutical field, the first part of the analysis concludes with a preliminary evaluation.

A. General principles

In any determination of whether a claimed invention is based on an "inventive step," European courts, the national patent offices, and the European Patent Organization (EPO) are guided by several sources of law. First, European authorities are, like their U.S. counterparts, bound by the TRIPS agreement, which expressly requires in Art. 27 (1) that any invention, whether products or processes, in all fields of technology must involve an inventive step.[26] Moreover, Article 3 of the EC Biotech Directive[27], which has a binding effect on the patent

[25] Of note: Many of the recent seminal UK decisions by the House of Lords and lower courts do not specifically concern DNA-related inventions. Yet, it will be shown below that the established principles are nevertheless of great importance for biopharmaceutical inventions relating to DNA, proteins and/or new formulations.

[26] *See* Art. 27 (1) in the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), to be found in Annex 1C of the Marrakesh Agreement Establishing the World Trade Organization, signed in Marrakesh, Morocco on 15 April 1994. *Cf.* in particular Art. 27 (1) fn. 5: "For the purposes of this Article, the terms "inventive step" and "capable of industrial application" may be deemed by a Member to be synonymous with the terms "non-obvious" and "useful" respectively."

[27] *Cf.* Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions OJ L 213, 30/07/1998 P. 0013 – 0021 (Art. 3 (1) stipulates: "For the purposes of this Directive, inventions which are new, which involve an inventive step and which are susceptible of

laws of all 27 member states of the European Union, expressly requires an inventive step for biotechnological inventions.

The EPO, however, grants patents by applying the European Patent Convention (EPC), which has been ratified by the currently 36 member states of the European Patent Organisation (EPOrg), including all 27 member states of the European Union.[28] In the EPC the criterion of inventive step is regulated in Article 52 (1), which merely establishes the requirement that all inventions must involve an inventive step to be patentable,[29] and Article 56, which refers more specifically to the concept of inventive step.[30] Article 56 EPC, which is binding on both the proceedings for a grant of a European patent and on national revocation proceedings against a European patent, requires *inter alia* that:

"An invention shall be considered as involving an inventive step if, having regard to the state of the art, it is not obvious to a person skilled in the art."

Thus, the EPC precludes patent protection for any novel invention that, in light of the state of the art, is obvious to a person skilled in the art. The "state of the art" comprises, as defined for the novelty requirement, in Art. 54 (2) EPC as *"everything made available to the public by means of written or oral description, by use, or in any other way, before the date of filing of the European patent application."* Yet novelty and inventive step are separate criteria. Novelty exists if there is any divergence between the invention and the known art. The "inventive step" criteria basically requires that there must be specific degree/quality of distinction from the prior art before a patent can be granted. This question only arises if there is novelty.[31]

One important difference is that in the assessment of Art. 54 the items of prior art are evaluated individually, whereas Art. 56 requires evaluation of the combined prior art, often called a "mosaic" of prior art, in order to examine which further development of the state of the art a skilled person would deduce from this combined material. The invention claimed must normally be considered as a whole. For a claim consisting of a "combination of features", this implies that an argument cannot be made that the separate features of the combination taken alone are known or obvious and that "therefore" the whole subject-matter claimed is obvious.[32] Generally speaking, the greater the number prior art references that

---

industrial application shall be patentable even if they concern a product consisting of or containing biological material or a process by means of which biological material is produced, processed or used.").

[28] A constantly updated list over the current contracting states, the extension states and the accession candidates is *available at* http://www.epo.org/about-us/epo/member-states.html (last visit 10 July 2009). The latest country to join the EPOrg was San Marino, which became a member on the 1st of July 2009. It should also be mentioned that although not formally bound by the Biotech Directive, the Administrative Council of the EPOrg. has by decision of 16 June 1999, which entered into force on September 1, 1999 (OJ 1999, 437 & 537) nevertheless incorporated specifically relevant provisions of the Biotech Directive into the EPC, now to be found in Chapter V, R. 26-29 EPC 2000.

[29] Article 52 (1) EPC, which has now been brought into compliance with the formulations in the TRIPS – agreement (EPC 2000) stipulates: "European patents shall be granted for any inventions, in all field of technology, provided that they are new, involve an inventive step and are susceptible of industrial application."

[30] Of note: Although a Community patent system has been debated for many years, there is still no EC patent available. Yet, the EPC not only mandates a harmonized substantive law on patent validity issues throughout Europe, but also provides a system trough which a bundle of identical national patents can be sought via a single prosecution process which administered by the EPO. Most patents for chemical compounds are granted via the EPO route. The validity of such patents can be challenged in central oppositions at the EPO. (National) patents can also be sought in national proceedings, which might proceed faster than via the EPO. These patents, including those granted by the EPO, can then be enforced and challenged in national courts.

[31] *Cf. Guidelines for Examination in the European Patent Office* (Version: April 2009), C-IV, 11.1, *available at* http://www.epo.org/patents/law/legal-texts/guidelines.html (last visit: 15 May 2009) (in the following: "EPO Examination Guidelines").

[32] *Cf.* EPO Examination Guidelines at C-IV, 11.5 (exempting aggregation or juxtaposition of features from this general principle).

must be combined, the greater the likelihood that an inventive step exists. An inventive step is present if the invention lies beyond the contemplation or capability of the skilled person who is presumed to have access to the state of the art in full.[33]

Although the wording of Article 56 EPC is kept very general and does not provide any definition of the term "obvious," which intuitively appears to be a very a subjective notion involving a matter of degree, its precise meaning was made slightly more predictable and objective by the EPO's case law and the Examination Guidelines.[34] Interestingly, a definition of the term "obvious" is provided at paragraph 11.4 of the current guidelines, which provides:

"The term 'obvious' means that which does not go beyond the normal progress of technology but merely follows plainly or logically from the prior art, i.e. something which does not involve the exercise of any skill or ability beyond that to be expected of the person skilled in the art."

Similar to the US, the characteristics and qualities that are conferred on the imaginative person skilled in the art are thus essential in the assessment of inventiveness. Hence one crucial question is: Who is the skilled person, and what would he have done?

In that context, an important point to note is that whether or not an invention is obvious is not a subjective matter despite its creative aspects. According to the EPO's practice only one correct decision exists with respect to an inventive step and the inventiveness cannot be simply determined in light of how much effort the applicant or patentee invested into the solution or what the inventor may think to have contributed to the art. Inventiveness must be decided objectively in the light of the technical problem which the invention has overcome, the technical problem being determined in the light of the disclosure of the application or patent together with that of the closest prior art. Normally, the invention lies in the solution of the problem, although sometimes the problem can be the decisive factor for establishing the inventive step, i.e. if the problem on which the invention is based cannot be derived from the state of the art.[35]

In order to apply these basic principles in the assessment of inventive step in an appropriate and consistent way, the EPO utilizes the so-called "problem- and solution-approach" which is constantly developed further through case law.[36]

1. The "problem –and-solution approach"

The EPO established the so called "problem-and-solution approach" to coordinate the various approaches to the inventive step as sessment that were applied by the member states

---

[33] *See.* Derk Visser, *The Annotated European Patent Convention*, Art. 56, note 1 (H. Tel Publisher, 17th ed. 2009) Another significant difference is, that for the purpose of examining inventive step the prior art does not include other European patent applications as referred to in Art. 54 (3) EPC. Thus the second sentence of article 56 provides further that, "if the state of the art also includes documents within the meaning of Art. 54, paragraph 3, these documents are not to be considered in deciding whether there has been an inventive step."

[34] EPO Examination Guidelines at part C-IV, 11 and Annex (April 2009); *Cf.* Visser, *supra* note 33 (adding that it is intentional that Art. 56 EPC does not give much guidance, leaving its interpretation, and therewith the standard of inventive step required, largely a matter of EPO policy.). Of note: The EPO has recently published a draft version of the future Guidelines for Examination applicable as of 01 April 2010. The changes to the Guidelines take, in particular, account of the decisions of the Administrative Council dated 25 March 2009 amending the Implementing Regulations to the European Patent Convention, CA/D 2/09 and CA/D 3/09 (OJ 5/2009, 296, 299). These Guidelines have no effect until this date. The final version of the new Guidelines will be published in all three official languages prior to 01 April 2010 in electronic format. A paper version will also be prepared, more information is *available at* http://www.epo.org/patents/law/legal-texts/guidelines-2010.html (last visit 14 February 2010).

[35] *See* case T 2/83 *"Simethicon-Tablette/Rider"* (concerning a conventional method of overcoming some previously unknown disadvantage in a known drug. In this case the invention was found in the problem itself.)

[36] *Cf.* Denis Schertenleib, *The Patentability and Protection of DNA-based Inventions in the EPO and the European Union*, EIPR 125, 130 (2003).

prior to the adoption of the EPC. By establishing a test that was assumed to be transparent, economical and objective the EPO hoped to bring a degree of certainty to the area.[37] The test is based on an image of the invention as a solution to a problem and regards research as an activity that endeavors to solve particular problems. Thus, an inventive step is seen as "a step from the technical problem to its solution."[38] As such, rather than asking whether an invention is obvious, the EPO tries to ascertain whether an invention provides to the addressed problem a solution that would have been obvious to the person skilled in the art. More positively stated, this implies that for an invention to be patentable, the solution must not have been obvious to the person skilled in the art at the priority date of the invention in question.[39] A detailed description on how the "problem-solution- approach" is to be applied in practice can be found in the *"Metal Refining/BASF"* decision of the EPO Technical Board of Appeal.[40] Pursuant to this decision the "problem-solution-approach" can be broken down into the following five component steps:

- First, the objectively prevailing closest state of the art and the technical effect that is achieved by it has to be established. The closest prior art usually concerns the same object and would have the most important technical features in common with the claimed invention.
- Second, the claimed invention and the technical effect achieved by it have to be ascertained.
- Third, after the establishment of these two extremes, the distinguishing features between the claimed teaching and the closest state of the art are to be evaluated.
- Fourth, subsequently, the objectively set and solved problem in order to go from the closest prior art to the claimed invention is to be defined.
- Fifth, an assessment is then to be made of whether or not, from the point of view of the skilled person, starting from the nearest state of the art, it was obvious to use the (distinguishing) features of the claimed teaching in order to solve the objective problem. If the solution to this objective technical problem is not obvious, then the inventive step hurdle is passed.

Over the years, the EPO's application of this test has proven to be a useful technique that is utilized in almost all kinds of situations. However, the test also exposes sources of error and has been criticized in literature and case law.[41] The following main aspects require a critical application of the problem solution approach:

First, one important factor complicating the examination of inventive step is that the requirement is always assessed after the date of priority. In determining the technical problem and evaluating the inventiveness of the solution, however, the retrospective element can be easily ignored. Particularly in rapidly evolving technologies, such as in the biotechnological

---

[37] G. Knesch, *Assessing Inventive Step in Examination and Opposition Proceedings at the EPO*, epi-Information 95, 98 (3/1994).

[38] *See* case T 26/81 *"ICI/Containers"*, OJ EPO 1982, 211.

[39] *Cf.* Bentley & Sherman, *supra* note 7, at 490.

[40] Case T 24/81 *"Metal Refining/BASF"*, OJ EPO 1983, 13; *cf.* the more recent decision in case T 641/00 *"Two identities/COMVIK"*, OJ EPO 2003, 319, para 5.

[41] F. Hagel and C. Menes, *Making Proper Use of the Problem-Solution Approach*, epi-Information, 14 (1/1995); R. Jehan, *The Problem and Solution Test in the Assessment of Inventive Step*, epi-Information, 69 (2/1995); Steven Crespi, *Recombinant Patents in Litigation – A Comparative Study of Some EPO and UK National Court Decisions* 28 IIC 603, 614 ff. (1997) (stating, that "the way the EPO applies the problem/solution approach to recombinant DNA patents sometimes seems rather artificial. This is because the claims often appear to present a mere 'shopping list' of what is obviously required to produce an obviously desirable result, rather than to embody some principle which constitutes the solution by which the result is achieved.") Compare also Willi Schickedanz, *Die rückschauende Betrachtung bei der Beurteilung der erfinderischen Tätigkeit*, GRUR 459, 460 (2001); Saito & Sweeney, *supra* note 1, at 4 (stating that even though hindsight is forbidden in Europe, determining the technical problem solved by the invention necessarily involves hindsight.). For the contrary opinion: R. Teschemacher, *Die Bewertung der erfinderischen Tätigkeit in 20 Jahren europäischer Praxis – Die Lösung eines Problems?*, epi-Information 25 (3/97) (who does not see any deficits if this approach is applied appropriately).

and pharmaceutical area, any decision-maker must therefore be constantly aware of the risk of reaching inappropriate conclusions with the benefit of hindsight knowledge.[42] In the course of an "ex post facto" analysis, the post-hoc observer is always smarter and tends to include common general knowledge that was only created subsequently or to transfer knowledge from the invention to the state of the art. Such a retrospective approach is expressly warned against according to the EPO Examination Guidelines[43] and it is prohibited by the established case law of the Technical Boards of Appeal (the Board). In order to avoid an artificial formulation of the state of the art and the problem that is based on hindsight knowledge, the Board has consistently held that the determination of the state of the art and the problem must remain free of elements that are inadmissibly derived from the solution of the invention claimed.[44] Thus, as a corrective measure, the historical surroundings and the background of the invention must be considered and this also includes indicative or secondary evidence.[45]

Second, the examination under the "problem-solution approach" necessarily leads to the question of whether the invention actually solves the technical problem. Yet, this must not result in adding a further requirement for patentability that goes beyond the industrial application requirement pursuant to Article 57, or the sufficient disclosure requirement under Article 83.[46]

While the Technical Board of Appeal has expressly acknowledged these concerns in various decisions, *Alcan/Aluminium alloys*[47] was particularly interesting, since it called into question more precisely specific aspects of the approach. Here, the Board pointed out that, while it was often taken for granted that the "problem-and-solution approach" was applicable in all situations, it should better be regarded as one of many possible approaches that could be adopted when assessing inventive step.[48] It was also underlined that no legal reason existed as to why all cases involving inventive step had to be judged by following a single approach.[49] Moreover, the Board expressly observed that, because the "problem-and-solution approach" relies on the results of a search made with actual knowledge of the invention, it is inherently based on hindsight, and therefore calls for care in its application in some circumstances. A further drawback, according to the Board in *Alcan*, is that the approach can result in

---

[42] *Cf.* Jürgen Kroher, in: Singer/Stauder, *The European Patent Convention: A Commentary*, Article 56, note 41 (Sweet & Maxwell/Heymanns, 3rd ed. 2003) (stating: "The rapid development of genetic engineering techniques in recent years means that in this area the risk of ex post facto analysis is particularly great.").

[43] *See* EPO Examination Guidelines at C-IV, 11.9.2 (providing "It should be remembered that an invention which at first sight appears obvious might in fact involve an inventive step. Once a new idea has been formulated it can often be shown theoretically how it might be arrived at, starting from something known, by a series of apparently easy steps. The examiner should be wary of ex post facto analysis of this kind…").

[44] *See* the headnotes in case T 223/92 *"Human γ-Interferon/GENENTECH"* and T 181/87 *"DNA transfer vector/The Regents of the University of California"*, 1990 OJ EPO 250. *See also* G.S.A. Szabo, *The Problem and Solution Approach in the European Patent Office* 26 IIC 457 (1995); G. Knesch, *Die erfinderische Tätigkeit – der Prüfungsansatz im EPA*, Mitteilungen der deutschen Patentanwälte (Mitt.), 311 ff. (2000).

[45] See Jürgen Kroher, *supra* note 42, Article 56, note 64 and 79.

[46] *Cf.* Jehan, *supra* note 41, at 69 ff.

[47] Case T 465/92 *"Alcan/Aluminium alloys"*, *available at* http://legal.european-patent-office.org/dg3/pdf/t920465ex1.pdf (last visit: February 22nd, 2009).

[48] *Id.* in the headnote ("The 'problem and solution approach' is no more than one possible route for the assessment of inventiveness. Accordingly, its use is not a *sine qua non* when deciding inventiveness under Article 56 EPC.").

[49] *Id.* at para 9.2 of the reasons ("The Board sees no legal basis for imposing on the organs of the EPO one particular method for the assessment of inventiveness under Article 56 EPC, where that Article has left the methods open. Rule 27(1)(c), which has been invoked as a basis for the problem and solution approach, is concerned solely with the formulation of the description, not the assessment of inventiveness under Article 56 EPC. Thus the problem and solution approach ought to be considered as one amongst other possible approaches, each of which has its own advantages and drawbacks.").

complicated multi-step reasoning where the facts are clear, either for or against inventiveness. Thus, if an invention breaks entirely new ground, saying that there is no close prior art may suffice, rather than constructing a problem based on what is tenuously regarded as the closest prior art.[50] For these reasons, the Board finally emphasized that the assessment of inventiveness required by Article 56 EPC should be primarily understood as a matter of judgment and that the investigation of inventiveness should therefore avoid formulating artificial and unrealistic technical problems.[51] Applying these findings to the facts of the case, the Board rejected the objections under Articles 54 and 56 EPC and held the claims in question to be patentable.

What the Technical Board of Appeal basically did in *Alcan* was to align the problem-solution-approach more closely with types of research under consideration. On the one hand, it has thus been argued that by modifying (and narrowing) the circumstances in which the test may be applied, the Board has actually served to strengthen the test and to provide further justification to it, which ultimately explains why the "problem – and -solution- approach" is still the main way in which the EPO determines inventive step.[52] On the other hand, this case clearly demonstrates that the Board of Appeal does not regard the "problem – and -solution-approach" as the only available test and that the EPO judges are very much aware of its flaws and the risk of hindsight determinations.

To address these problems and to achieve an accurate application of the "problem solution approach" patent examiners at the EPO must follow various rules that are continuously developed through case law. These cases are often concerned with the proper identification of the objective state of the art, the treatment of technical and non-technical features or the proper assessment of the problem and its solution.[53] Moreover, the patent examiners and judges at the EPO apply a particular test when they have to decide the ultimate question under the problem-solution-approach, i.e. whether or not the solution found by the applicant is obvious to a person skilled in the art. As indicated above, any answer to this crucial question requires every possible precaution to avoid an "ex-post-facto" analysis. In order to come to grips with these inherent problems, the EPO's Technical Board of Appeal developed in its case law the so called "could-would"-approach.

---

[50] *Id.* at para 9.5 of the reasons.

[51] *Id.* at para 9.6 (adding: "As reflected by some of the decisions of the Boards of Appeal, the problem and solution approach can entail the exercise of judgment in deciding what is to be treated as the so-called "objective" problem. Once that problem has been identified, in some cases little further judgment may be needed to decide the issue of obviousness. Nevertheless, problem and solution analysis does not remove the element of judgment inherent in the assessment of inventiveness, but rather displaces it from the task set by the EPC, to another task which is inessential to Article 56 EPC. In that connection the Board sees a welcome trend in some recent unreported decisions, which have emphasised that the investigation of inventiveness should avoid formulating artificial and unrealistic technical problems, and should normally start from the technical problem identified in the patent in suit (cf. T 495/91, 20 July 1993; T 246/91, 14 September 1993; and T 741/91, 22 September 1993).").

[52] *Cf.* Bentley and Sherman, *supra* note 7, at 490.

[53] EPO case law established *inter alia* that: - the patent specification is the starting point for the determination of the problem (T 741/91 of 22 September 1993); - the problem is determined according to objective criteria without any subjective considerations (T 13/84, OJ 1986, 253); - the starting point is the objectively closest state of the art (T 334/92 of 23 March 1994, *cf.* T 824/05 of 28 Sept. 2007, which defined the closest state of the art as representing the most promising springboard towards the invention); - the technical problem is to be worded in such a way that it does not contain any approaches to the solution (*see* T 184/89 of 25 February 1992); - the assessment of the inventive step of a business-related method may be possible without a preliminary clear-cut separation between business-related features and technical features (*cf.* T 912/05 of 15 April 2008); and that, as a matter of principle, patentability requires the solution of the problem stated, although the problem- solution approach must not introduce an additional requirement for patentability that goes beyond Art. 57 (T 346/89 of 21 June 1989) etc....; *cf.* Guidelines for Examination in the EPO Guidelines (2009), part C, IV-27.

2. The "could – would" approach and the "obvious to try" issue

Pursuant to this approach an invention is not obvious merely because the average skilled person with access to the entire state of the art at the time of priority *could* have achieved the same invention by adapting, modifying or combining the closest prior art,[54] but whether he *would* have done so because the prior art incited him to do so in the hope of solving the objective technical problem or in expectation of some improvement or advantage.[55] This distinction is very important, since there are often a variety of methods which inventors *could* have used in order to arrive at an invention. The "could-would" approach, however, makes clear that the fact that a solution is technically feasible does not mean that the person skilled in the art actually *would* have used these methods and that it would have been obvious for the skilled person to embark on this solution.[56]

In that way, the EPO's case law recognizes that in some instances it might be much more difficult to actually succeed in a process or make a specific substance available than in other cases. This is particularly true in highly unpredictable, relatively unexplored and complex technologies, such as DNA and protein related technology.[57] Various complicated phenomenona, such as the redundancy of the genetic code, gene splicing, complex interactions of proteins and DNA, as well as other biological mechanism that are involved in cellular gene expression, imply that molecular biologists are often confronted with many possible solutions with the prior art pointing only very vaguely in one direction. Thus, in many cases uncertainty still remains as to which path would lead to success. In other words, the process of finding the right solution often involves a combination of many intermediate steps. Although working with or combining previously known processes or methods within a new field of application might have been "obvious to try", the process might still have involved many difficulties. Some chosen paths, which later proved to be successful, might previously have been considered by the majority of scientists to be the least attractive or most improbable route to success. Therefore, the EPO generally finds a technical solution obvious only if it would have been obvious to combine, or obvious to try to combine, the documents representing the previous state of the art, *and* if the successful combination of the features was foreseeable and/or lead to previously expected results.

---

[54] What matters with a combination is not whether the individual features of the combination are known or obvious, but the examination of the combination as a whole, compare EPO T 37/85- *Mannesmann*, OJ 1988, 86: "In assessing the inventive step involved in an invention based on a combination of features one must consider whether or not the state of the art was such as to suggest to a skilled person precisely the combination of features claimed. The fact that an individual feature or a number of features were known does not conclusively show the obviousness of a combination." Yet, pursuant to the EPO Guidelines C.IV, 11.8 a combination of two documents of the state of the art is obvious if one document makes a clear unmistakable reference to the other. Also, as a rule it is obvious to combine the teaching of one or more documents with the common general knowledge of the average skilled person, e.g. as documented in a well-known specialist book or dictionary with a prior art document. Further, no inventive step is present if, for lack of other alternatives, the prior art leads the skilled person to the claimed teaching in a "one-way street situation" (*cf.* T 192/82, OJ 1984, 415- *Bayer*).

[55] This significant difference between *could* and *would* is part of the established case law of the EPO's Boards of Appeal. *See* cases T 2/83 "*Simethicon Tablet/Rider*", OJ EPO 1984, 265; T 455/91 "*Expression in Hefe/GENENTECH*", ABl. 1995, 684, nr. 5.1.3.3 and 5.1.3.4 of the reasons; P. Lançon, *Die Rechtsprechung der Beschwerdekammer des EPA* 1994 bis 1996 – ein Überblick, GRUR 227, 229 (1998); *cf.* EPO Guidelines, C IV – 11.7.3.

[56] Jürgen Kroher, in: Singer/Stauder, *Europäisches Patentübereinkommen*, Rdnr. 52 – 44 (4. Aufl., Heymanns 2007) (commentary in German), cf. Jürgen Kroher, *supra* note 42, Article 56, note 60.

[57] However, as it will be demonstrated in the following chapters, this technology has during the recent years become more predictable than it was just 10 years ago.

EPO case law further clarifies that absolute predictability is not required for a finding of obviousness. For example, in T 249/88 "*Monsanto/Milk Production*"[58] the EPO Technical Board of Appeal found:

> *The necessity of experimentally confirming a reasonably expected result does not render an invention unobvious. Absolute predictability, especially in the field of biologically active chemical compounds, is rather exceptional, but inventions relating to such compounds and their administration to living organisms may nevertheless be obvious. However, if such administration were to lead to an unexpected result, which is not the case here, this might provide a basis for demonstrating non-obviousness.*[59]

In accordance with the well-established case law of the Boards of Appeal, a course of action can therefore be considered obvious within the meaning of Article 56 EPC, if the skilled person *would* have carried it out with a *reasonable* expectation of some improvement or advantage.[60] In other words, obviousness is present not only when the results are clearly predictable but also when achieving the invention in a specific way is "obvious to try" *and* involves a "reasonable expectation of success."[61] This approach has been called the "obvious to try with a reasonable expectation of success"- doctrine.[62] It was applied in connection with the "could-would" approach in a series of cases where obviousness was assessed pursuant to Article 56 EPC.[63]

---

[58] Case T 249/88 "*Monsanto/Milk Production*", (1996) E.P.O.R., at 29, 30 (Technical Bd. App. 1989) (involving the patentability of a method increasing the milk production of a cow).

[59] *Id.* at 35. As for the US, compare the CAFC's famous statement in *In re O'Farrell*, 853 F.2d 894, 903-04 (Fed.Cir. 1988) ("It is true that this court and its predecessors have repeatedly emphasized that "obvious to try" is not the standard under §103. However, the meaning of this maxim is sometimes lost. Any invention that would in fact have been obvious under §103 would also have been, in a sense, obvious to try. The question is: when is an invention that was obvious to try nevertheless nonobvious? The admonition that "obvious to try" is not the standard under § 103 has been directed mainly at two kinds of error. In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. In others, what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it. Obviousness does not require absolute predictability of success. Indeed, for many inventions that seem quite obvious, there is no absolute predictability of success until the invention is reduced to practice. There is always at least a possibility of unexpected results, that would then provide an objective basis for showing that the invention, although apparently obvious, was in law nonobvious. For obviousness under § 103, all that is required is a reasonable expectation of success." (Citations omitted)).

[60] Case T 2/83 "*Simethicon Tablet/Rider*", OJ EPO 1984, 265, point 7 of the reasons.

[61] *See* the subsequent confirmation of this rule in e.g. case T 1241/03 "*Human growth hormone/GENENTECH*" (1 September 2005), para. 31.

[62] In the "*Monsanto/Milk Production*" case from 1988 (*see supra* note 58) the EPO Technical Board of Appeal therefore appeared to adopt, a least in dicta, a test which was very similar to the previous US decision in *In re O'Farrell* (*see supra* note 14), where the CAFC set forth and developed the "reasonable expectation of success" standard .

[63] Cases T 60/89 "*Fusionsproteine/HARVARD*", ABl. EPA 1992, 268, nr. 3.2.5 of the reasons; T 223/92 "*Human γ-Interferon/GENENTECH*" (not published in ABl.), nr. 5.4, 5.12 of the reasons; T 455/91 "*Expression in Hefe/GENENTECH*", ABl. 1995, 684, nr. 5.1.3.8 of the reasons. In all these cases it was held that the essential question is, whether the average skilled person would have tried the same methods at the time of priority to solve the technical problem with a "reasonable expectation of success."

3. The notion of a "reasonable expectation of success"

It is then crucial to more precisely determine what should be considered a "reasonable expectation of success" - a notion which not only seems to be highly dependant on the available technology and the general qualities of the person skilled in the art but also on its more specific definition in various situations.

In a series of subsequent, mostly biotech-related cases, such as T 0877/90[64], T 694/92[65], T 296/93[66], 923/92[67], T 386/94[68] and T 207/94[69], the Technical Board of Appeal provided a more precise definition of what is to be understood as a "reasonable expectation of success" in the biotechnological field. For example, in T 0877/90 *"Hooper Trading Co. N.V. / T-cell growth factor,"* the Board found that an invention was not obvious where the skilled worker required skills beyond common general knowledge and where the amount of trial and error which could be expected of the skilled worker was excessive. Then, in T 296/93 *"Hepatitis B virus antigen production/BIOGEN,"* the Board underlined that trials in a new, uncertain region are seldom accompanied by "reasonable expectation of success" and that the mere "hope to succeed" should not be misconstrued as a "reasonable expectation of success":

> The fact that other person (or teams) were also working on the same project might suggest that it was 'obvious to try' or that it was 'an interesting area to explore', but it does not necessarily imply that there was a 'reasonable expectation of success'. 'A reasonable expectation of success' which should not be confused with the understandable 'hope to succeed' implies the ability of the skilled person to reasonably predict, on the basis of the existing knowledge before the starting of a research project, a successful conclusion of the research project within acceptable time limits. The more unexplored a technical field of research is, the more difficult is the making of predictions about its successful conclusion and, consequently, the lower the expectation of success.[70]

The Board's case law also confirms that a competition between different groups of researchers hoping to succeed with a specific project, sometimes in the context of a "race to the patent office," does not necessarily allow for the conclusion that there must have been a reasonable expectation of success. In other words, whether there was a race and who won it is basically irrelevant.[71]

---

[64] Case T 0877/90 *"Hooper Trading Co. noteV. / T-cell growth factor"* (1993) EPOR 6.

[65] Case T 694/92 *"Modifying plant cells/MYCOGEN"* (8 May 1996), 1997 OJ EPO 408 (in this case, a prior publication disclosed unsuccessful attempts and continuing attempts to achieve a particular result. The claimed subject matter was considered inventive despite the prior art because "reasonable expectation of success" is not to be confused with "the understandable hope to succeed").

[66] Case T 296/93 *"Hepatitis B virus antigen production/BIOGEN"* (28 July 1994), 1995 OJ EPO 627. *Cf.* Sven J.R. Bostyn, Patenting DNA Sequences (Polynucleotides) and Scope of Protection in the European Union: An Evaluation (Luxemburg, European Communities 2004), 19 (stating that T 296/93 illustrated, that "The standard is whether an invention is obvious or not, and not whether it is obvious to try.").

[67] Case T 923/92 "*Human t-PA/Genentech"* (8 November 1995), 1996 OJ EPO 564.

[68] Case T 386/94 "*Chymosin/UNILEVER"* (11 January 1996), *cf.* the summary in section II. B. 1.

[69] Case T 207/94 "*Human beta-interferon/BIOGEN"* (8 April 1997), 1999 OJ EPO 273, *see* the headnote ("In case the expression of a cloned DNA in a chosen foreign host constitutes the subject-matter of the claimed invention, reasonable expectation of success may be evaluated only by taking into account real difficulties related to that step. Hence, in order to be considered, any allegation of features putting in jeopardy reasonable expectation of success must be based upon technical facts.") *See also* at para 31 ("the hope to succeed" should not be misconstrued as a "reasonable expectation of success".)

[70] Case T 296/93, *supra* note 66, at para 7.4.4.

[71] *See* Hans-Rainer Jaenichen, Leslie McDonell, James F. Haley & Yoshinori Hosoda, *From Clones to Claims* (4th edition 2006), para 17.1.3. (referring to case T 386/94 *"Chymosin/UNILEVER"* (11 January 1996), para 43 and adding that "(T)his issue cam up again in another cloning case where the Board stated; that obviousness of a

In T 923/92 *"Human t-PA/Genentech"*, the Board had to decide whether the skilled person would have attempted, with reasonable expectation of success, to produce cDNA coding for human t-PA (tissue Plasminogen Activator) or whether, in this instance, he would have known from his technical knowledge, before even embarking on the research, that he would be able to complete his project within acceptable time-limits. Referring to its previous decision in T 816/90, the Board held that:

> "[e]ven when it is possible to theoretically conceive a straightforward approach to solve a specific technical problem, the skilled person might be confronted with unexpected difficulties when trying to put the conceived strategy into practice".[72]

The Board continued that, although hoping to succeed, the skilled person embarking on this project would have known that its successful conclusion depended not only on technical skill in putting into practice the sequence of precise steps of the theoretical experimental protocol, but also to a large extent on the ability to take the right decisions along the way whenever a difficult experimental situation so required.[73] Under these circumstances, the skilled person could *not* be said to have had a "reasonable expectation of success." Moreover, where there is some prejudice against following a particular course or something negatively influences the degree of confidence of the skilled person in a successful outcome of an experiment, the invention may not be obvious.[74]

On the other hand, the Board also made clear that the mere fact that a claimed biotechnological invention was the result of work requiring a considerable amount of time and money does not necessarily imply that the hypothetical person skilled in the art would not have arrived at the same solution. This is particularly true, if the necessary work was comparatively uncomplicated or routine and the person skilled in the art had from the start a "reasonable expectation" to (at one point) succeed with this work.[75]

Under such circumstances, a patent applicant could neither sensibly argue that he or she had no particular expectations of any sort when going through the stages that finally led to the claimed invention, but was merely curious to see whether a result could be achieved. Such a "try and see" attitude does not equate to an absence of reasonable expectation of success, as clarified by the Board in T 333/97 *"Somatic changes/Monsanto"*[76]. In denying an inventive step the Board held:

> The suggestion in ... and the optimistic tone of ... *(the prior art)* would have given the skilled person an incentive to try to introduce in a plant a DNA to be transcribed into a negative strand RNA having sufficient complementarity to a given target pathogenic RNA strand. These are exactly the measures proposed .... (*in the claim at issue*)...as a solution to the underlying technical problem, and performing them merely required the application of

---

DNA sequence cannot be judged on the basis of whether or not one or more teams were working in parallel at the same project or whether or not a team was working under more favorable conditions than another team; T 637/97...", *cf.* case T 296/93).

[72] Case T 923/92, *supra* note 67, at para. 51.

[73] *Id.* at para 57 (stating further: "All the above factors would have influenced the degree of confidence of the skilled person in the successful conclusion of cloning and expressing human t-PA. Knowing that a cDNA library could not be better than the mRNA from which it was derived and faced with the various uncertainties depicted above, the skilled person would not have expected the theoretically straighforward route (*cf.* point 55 supra) to be easily put into practice.").

[74] Case T 694/92 "*Modifying plant cells/MYCOGEN*" (8 May 1996), 1997 OJ EPO 408.

[75] *See* case T 1396/06 *"HLA Binding Peptides/EPIMMUNE"* (31 May 2007), *cf. infra* note *167; see also* case T 386/94, *supra* note 68, in the headnote ("Inventive step may be acknowledged in the field of gene technology if there is no reasonable expectation of success that the cloning and expression of a given gene can be carried out. However, in a case where, at the priority date, a skilled person can expect to perform the cloning and expression of a gene in a fairly straightforward manner, and the cloning and expression, although requiring much work, does not pose such problems as to prove that the expectation of success was ill-founded, inventive step cannot be acknowledged.").

[76] *See case* T 333/97 "*Somatic changes/Monsanto*" (5 October 2000).

> techniques and knowledge available at the time of the invention, no particular ways or strategies being proposed by the patent in suit. In the absence of evidence of real difficulties which would be encountered, the skilled person, when following the indicated route, would have had either some expectations of success, or, at worst, no particular expectations of any sort, but merely the curiosity to see whether a result could be achieved. The latter situation, however, does not equate with an absence of reasonable expectation of success.[77]

Last but not least, note that the "reasonable expectation of success" test might be held to be inapplicable in the inventive-step assessment of a claimed invention relating to predominantly uncontrollable experiments. This can be derived from the decision in T 737/96 *"Astaxanthin/DSM."*[78] Considering the inventiveness of claim 1 in the main request concerning a method of preparation of a specific yeast cell (Phaffia rhodozyma) through mutagenesis,[79] the Board opined that an attempt to evaluate the "expectation of success" of a random technique, such as mutagenesis where results depend on chance events, was *not* appropriate.[80] The Court explained further that:

> This is because the skilled person knows that, unless a specific selection method can be developed, which is not the case in the patent in suit, perseverance and chance play a key role in the achievement of success, as no form of control can be exerted over the mutation events. Under these circumstances, like eg in a lottery game, the expectation of success always ranges irrationally from nil to high, so it cannot be evaluated in a rational manner based on technical facts. This is at variance with technical situations in which more predictable methods are relied upon to solve a particular problem, such as the methods of genetic engineering like cloning and/or expressing a DNA sequence. In such situations, it is often possible to make rationally predictions about the possibilities of success, and the evaluation of the "reasonable expectation of success" is then a meaningful and reliable tool in the assessment of inventive step (cf T 694/92 supra, see in particular point 28.7 of the reasons).[81]

Also important to realize, however, is that this statement certainly does *not* allow the conclusion that every technical contribution that is the result of research where mere chances or coincidences are decisive automatically involves (or precludes) an inventive step. Instead the Board seemed to focus on a more general, overall examination in order to determine the inventiveness of the claimed preparation method. In doing so, the Board particularly evaluated the extent to which the claimed method actually contributed to the progress of the scientific and technical state of the art.[82] In summary, the Board held in this case that the

---

[77] *Id.* at para 13 (the inventive step was then denied at para 14), *see also* the confirmation of this principle in case T 1045/98 *"Eosinophilia/SCHERING"*, para 17 (22 October 2001), and in case T 1396/06, *supra* note 75, at para 7. Concerning recent cases where the Board acknowledged an inventive step since a person skilled in the art adopting a "try and see" attitude would not have arrived at the invention. *cf.* case T 759/03, *FIV/St. Vincent's Institute, et al.* (17 August 2006), *see infra note 149; and* Case T 1599/06, *Mycobacterium vaccinating agent/UNIVERSITY OF CALIFORNIA* (13 September 2007), *see infra* note *153*.

[78] Case T 737/96 *"Astaxanthin/DSM"* (9 March 2000).

[79] *Id.* at paras. *1-10* (The technical problem to be solved in the light of the prior art was defined as the provision of Phaffia rhodozyma mutants producing increased yields of the carotenoid pigment astaxanthin (para 5). As a solution, claim 1 essentially proposes a method of preparation of a Phaffia rhodozyma yeast cell which, under defined conditions, produces astaxanthin in an amount of at least 600 µg per g of yeast dry matter, said method comprising treating a naturally occurring Phaffia rhodozyma yeast cell with specific mutagens (para 6). In para 8, the relevant question in relation to inventive step was identified as follows: What measures would the skilled person faced with the stated technical problem have considered adopting, in the light of the quoted prior art and common general knowledge, and would these measure have included a method covered by claim 1?).

[80] *Id.* at para. 11.

[81] *Id.*

[82] *Id.* at paras. 8-10 & 12 (at para 12 the Board held in particular that the feature "produces astaxanthin in an amount of at least 600 µg per g of yeast dry matter", could not *per se* contribute to inventive step of the broadly formulated method claim 1, since the inventors had not contributed a specific mutagenesis method whereby the skilled person can take a naturally occurring Phaffia rhodozyma strain and isolate mutants with the same feature

measures adopted by a skilled person would have included the claimed method as covered by claim 1 in the main request. Thus, the Board decided that claim 1 lacked an inventive step and was not allowable under Article 56 EPC.[83]

4. Secondary indicia & the (in)significance of structural predictability

As it was already indicated by T 249/88 "*Monsanto/Milk Production*"[84], EPO case law further acknowledges secondary indicia, which in certain circumstances could be regarded as a sign of inventive step. Such indicia may be referred to in order to strengthen or weaken arguments in the problem and solution approach. Yet, as indicated by their name, their significance is, at least formally, of a secondary nature.[85] Secondary indicia alone do not suffice to show inventive step but may principally point towards the possible presence of an inventive step, e.g. by properly forming a basis for the definition of the problem that the claimed invention sets out to solve. Consequently, any argument in support of an inventive step should start with an examination of the prior art by a person skilled in the art, not with secondary indicia.[86]

Current case law, however, illustrates that secondary indicia nevertheless play a "primary" role when arguing for the inventive step of DNA-related inventions at the EPO. One reason for this is that the EPO has consistently considered "structural non-obviousness" arguments alone to be *in*sufficient for successfully arguing for the inventiveness of the provision of a particular DNA sequence that could have been isolated without inventive effort and with a reasonable expectation of success (i.e. according to routine cloning and screening methods).[87] In such a case the inventor must also demonstrate some unexpected advantageous properties of the claimed compound such as a claimed DNA sequence.[88] Because isolation methods have become ever more routine due to rapid technological development, the importance of "secondary indicia" has gradually increased in the past years. As it will be discussed further in Part II, the Supreme Court's rejection of the strict *In re Deuel* doctrine in

---

without having to rely only on chance events. Moreover, the Board reminded that the said feature is the generalisation of a characteristic found in relation to specific isolates obtained by chance. In the absence of the description of a fairly reliable method for obtaining Phaffia rhodozyma mutants displaying said feature, without having to rely again on perseverance and chance, the said feature amounts to arbitrarily setting a minimum yield to be achieved by the skilled reader which per se is an obvious desideratum in view of the prior art. The Board then emphasized that in such technical circumstances, it is rather the actual isolation of a mutant indeed having such characteristics which can be surprising, not the theoretical possibility of achieving one).

[83] *Id.* at para 13 (subsequently, however, the Board acknowledged the patentability of the auxiliary requests relating to product claims on specific mutants. The Board found at paragraph 17 that these mutants, albeit achieved by routine mutagenesis techniques, had surprising properties (i.e. they were capable of producing astaxanthin with yields above 600 µg per g of yeast dry matter) which justify the recognition of an inventive step).

[84] Case T 249/88, (1996) E.P.O.R., at 29, 30, *see also supra* notes 58 & 59.

[85] *Cf.* Visser, *supra* note 33, at Art. 56, note 7.

[86] *Id.*

[87] *See* Jaenichen et al., *supra* note 71, at para 17.1.4 (explaining in more detail the relationship between the inventive step requirement and the EPO's pragmatic approach when assessing enabling disclosure (rather broad claims are allowable and no structural predictability is not always necessary)).

[88] *Id.* (emphasizing that these properties must be truly surprising and adding that "Because of the explained evident context care has to be taken in the defense of inventive step so as to avoid providing a basis for lack of enabling disclosure attacks, see section 9.1.2, supra. Thus when an animal model is relied on for providing experimental evidence for a second medical use of a substance, related animal models in the prior art may well render the second medical use invention obvious; T 1045/98 (section 18.10.22, infra).").

KSR v. Teleflex and the CAFC decision in *In re Kubin* implies that this is now also very much true in the United States.[89]

Similar to the U.S.,[90] the secondary indicia that may be considered can include various factors,[91] such as surprising properties, a long felt need, more simple solutions without sacrificing quality, contrary prejudices in the art, and under certain circumstances even commercial success[92] and the immediate adoption of the patent's teaching by market competitors[93]. Due to the fact that the EPO, like U.S. courts and the USPTO, treats DNA and protein sequences similar to chemical compounds, albeit complex ones,[94] the Technical Board of Appeal particularly regards unexpected advantageous technical effects or properties, such as beneficial qualities that were not suggested by the prior art and not foreseeable to the person skilled in the art at the relevant date, as a sign of inventiveness.[95]

In T 247/97 *"Augmentation materials from the placenta/INSTITUT CLAYTON DE LA RECHERCHE"* the Board pointed out very clearly that in the case of a product claim any properties relied on for establishing inventive step must *really* be unexpected and advantageous.[96] This conclusion was already supported by the Board in T 886/91 *"Hepatitis B virus/ BIOGEN INC."* and it is also in line with the EPO's practice in the field of chemistry.[97] The decision in T 111/00 *"Monokine/FARBER"*, which is discussed above at I.B.2., made this point very explicitly in the area of DNA cloning.[98]

According to the established jurisprudence of the Boards of Appeals, it is then further important that such properties or effects can be properly demonstrated by means of *truly comparable* results. Yet, the only suitable comparative tests are those concerned with the structurally closest state of the art to the invention, because only here the factor of unexpectedness is to be sought.[99] The nature of the comparison with the closest state of the

---

[89] For a more detailed discussion of pre KSR obviousness case law in the US and a discussion of the doctrine of structural similarity as it was applied by the CAFC in *In re Deuel*, *see* Timo Minssen, Patenting Human DNA Sequences in Europe and the US, Licentiate thesis, Lund University (2005), 111-33 & Timo Minssen, *supra* note 23.

[90] As for the US, compare e.g. the "secondary factors" set out in *Graham v. Deere, 383 U.S.* 1, 17-18 (1966) and their further development in case law like *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538-39 (Fed. Cir. 1983), which raised them to "objective factors".

[91] A more comprehensive overview of various potential secondary indicia that might be considered by the Board is provided in *Case Law of the Boards of Appeal of the European Patent Office*, at I. D.9. (5th Ed. 2006). *See also* Kroher, *supra* note 56, at Artikel 56, Rdnr. 68-115 (commentary in German). For further examples from the biotechnological field, see above under I.B.3.

[92] As in the US commercial success alone is not by itself an indicator of inventive step. It needs to be coupled with a long-felt need and evidence that the commercial success derives from technical features and not from other influences such as advertising, *cf.* headnotes in case T 1212/01 *"Pyrazolopyrimidinones for the treatment of impotence/PFIZER LIMITED ET AL"* (3 February 2005).

[93] *See* the recent decision in case T 252/06 *"Flaschendispenser"* (6 May 2008 – in German, no headword yet).

[94] As for the EPO *see* case T 301/87 *"Biogen/Recombinant DNA"*, EPOR 190, 207-11; *see also "Howard Florey/Relaxin"* (1995) E.P.O.R. 541. As for the US *see Amgen v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1213 (Fed. Cir. 1990); cert. denied, 502 US 856 (1991) (holding "A gene is a chemical compound, albeit a complex one ....").

[95] As for surprising effects in chemical case law at the EPO *see case* T 20/83 (17 March 1983 – no headnote); as for the US, *see In re Chupp*, 816 F.2d 643 (Fed. Cir. 1987) and *In re Papesch*, 816 F.2d at 643 (C.C.P.A. 1963). That secondary evidence can rebut an obvious finding based on structural similarity was inter alia confirmed by *In re Dillon*, 919 F.2d 688, 692-93 (Fed. Cir. 1990) (the application of these principles in DNA-related cases will be discussed further below).

[96] Case T 247/97 *"Augmentation materials from the placenta/INSTITUT CLAYTON DE LA RECHERCHE"* (29 January 2002), at paras 3-9.

[97] Case T 886/91 *"Hepatitis B virus/ BIOGEN INC."* (16 June 1994).

[98] Jaenichen et al., *supra* note 71, at para 17.1.4.

[99] *See case* T 181/82 *"Spiro compounds"* (28 February 1984), OJ EPO 1984, 401, in headnote 1; *see also* case T 955/96 *"Microspheres/WEST PHARMACEUTICAL SERVICES"* (19 April 2001), at para 5.10.

art should be such that any alleged advantages or beneficial effects are convincingly and unambiguously shown to originate from the distinguishing feature of the invention *vis à vis* the closest state of the art.[100] In T 234/03 *"Jet ink composition/VIDEOJET TECHNOLOGIES"*[101], the Board stated that to be relevant for demonstrating that a technical improvement is achieved in comparison with the closest state of the art, any comparative test presented for that purpose must be reproducible on the basis of the information provided, thereby rendering the results of such tests directly verifiable.[102] In particular, that requirement implies that the procedure to perform the test relies on quantitative information enabling the person skilled in the art to reliably and validly reproduce it. Vague and imprecise operating instructions render the test inappropriate and thus irrelevant.[103]

Moreover, the Board has held that if it would have been obvious for a skilled person in light of the state of the art to arrive at something falling within the terms of a claim (e.g. due to a lack of alternatives thereby creating a "one-way street" situation), the unexpected additional effect is merely a *bonus effect* that does not confer inventiveness on the claimed subject-matter.[104]

5. Selection inventions

So called "selection patents" represent a specific aspect of chemical and biopharmaceutical patenting. The basic idea behind such patents is that if somebody establishes that the selection of a particular compound or compounds provides previously unknown advantages not shared by other members of the broadly disclosed class, such separate contribution to knowledge merits its own patent protection. Unfortunately, however, the legal basis for such inventions is somewhat unclear and seems to vary between the national patent systems and the EPO, which has to some extent adopted the general concept but has interpreted it in a somewhat different way.[105] Most of the substantial issues concerning selection inventions would initially have to be addressed in the examination of the novelty criteria. Yet, it would then still be necessary to determine whether a particular selection that is claimed for the first time was actually also inventive. As for the inventive step assessment the current EPO Examination guidelines provide the following:

> The subject-matter of selection inventions differs from the closest prior art in that it represents selected sub-sets or sub-ranges. If this selection is connected to a particular technical effect, and if no hints exist leading the skilled person to the selection, then an inventive step is accepted (this technical effect occurring within the selected range may also be the same effect as attained with the broader known range, but to an unexpected degree). The criterion of "seriously contemplating" mentioned in connection with the test for novelty of overlapping ranges should not be confused with the assessment of inventive step. For inventive step, it has to be considered whether the skilled person would have made the selection or would have

---

[100] *See* case T 197/86 (4 February 1988 - no headword), OJ EPO 1989, 371, at para 6.1.3; *see also* T 378/03 *"Cyclic peroxides/AKZO NOBEL"* (4 July 2006), at para. 3.4.2 & 3.4.6 ff.; *see also* the "plausibility"- discussion below.

[101] Case T 234/03 *"Jet ink composition/VIDEOJET TECHNOLOGIES"* (18 May 2006).

[102] *Id.* at para 8.4.4; following T 494/99 *"Hard Candy/CERESTAR"* (19 February 2003), at para 5.2.

[103] *Id.*; *cf.* the discussion of case T 1336/04 *"Cellulase/NOVOZYME"* (9 March 2006), *infra* note 270.

[104] Guidelines for Examination in the European Patent Office (April 2009), part C, Chapter IV, 11.9.2 - 11.9.3, referring to T 231/97 *"Emissionsarme Dispersionsfarben/CLARIANT"* (21 March 2000) and T 192/82, OJ 9/1984, 415 (22 March 1984). For further case law references *see* Visser, *supra* note 33, at para 7.4 (explaining that in a "one-way street" situation the skilled person only has one available approach for modifying the closest prior art to choose from).

[105] Trevor Cook, *Pharmaceuticals, Biotechnology and the Law*, at paras 5.69-5.74 (LexisNexis, 2nd edition 2009) (referring inter alia to the first development of the concept in the UK in IG Farbenindustrie AG's Patent 47 RPC 289 and pointing out (partly previous) differences in EPO, UK and German case law).

> chosen the overlapping range in the hope of solving the underlying technical problem or in expectation of some improvement or advantage. If the answer is negative, then the claimed matter involves an inventive step.[106]

While most of the reported selection patent cases at the EPO tend to involve attempts to patent selections from a numerical range of a particular parameter, rather than the selection of certain compounds, many of the more instructive cases of the second type involve optical isomers and so called "formulation"-inventions.[107] Some recent national decisions relating to these cases, will be discussed subsequently in Part II, because they have special impact on the novel developments concerning the national "selection invention" and "obvious to try" standards.[108]

As for DNA-related inventions, artificially mutated genes may potentially be considered to be an inventive selection invention if the mutated gene has a demonstrable unexpected advantage over the naturally occurring gene. Yet in accordance with the AGREVO principles (cf. Section II, C. 1., below), the advantage (i.e. the additional technical effect) of such mutated genes over the naturally occurring gene would have to be common to substantially all of the mutations selected and claimed for that particular gene.[109]

Notably, the "selection invention" criteria can also be applied to the specific combination of probes on a microarray. For example, if the exact combination of probes on a microarray results in a more accurate detection and/or a more precise diagnosis than the use of the probes individually, then the particular selection of probes may provide a surprising effect and an inventive step. Moreover, this surprising effect may confer a unity of invention to the probe combination. In that regard it is further important to pay particular attention to the EPO examination guidelines which provide at para C-IV, 11.5:[110]

> The invention claimed must normally be considered as a whole. When a claim consists of a "combination of features", it is not correct to argue that the separate features of the combination taken by themselves are known or obvious and that "therefore" the whole subject-matter claimed is obvious. However, where the claim is merely an "aggregation or juxtaposition of features" and not a true combination, it is enough to show that the individual features are obvious to prove that the aggregation of features does not involve an inventive step (see IV, 11.7.2, last paragraph). A set of technical features is regarded as a combination of features if the functional interaction between the features achieves a combined technical effect which is different from, e.g. greater than, the sum of the technical effects of the

---

[106] *See* Guidelines for Examination in the European Patent Office (2009), C-IV, 11.11.

[107] *See* Cook, *supra* note 105, at 5.71 (providing a more detailed explanation of "optical isomers", "racemic mixtures" and "enatiomers" at 5.75 and describing the significance of novel "enantiomers" for the pharmaceutical industry). Another more instructive case that did not concern optical isomers but inventive pharmaceutical compound selections is T 0007/86 "*DRACO/Xanthines*" (1988), OJ EPO 381.

[108] Part II will refer to recent decisions from the UK (and Germany, which previously had an extremely restrictive view with regard to selection inventions) indicating that national case law has with regard to some aspects, and in particular the selection invention and "obvious to try" issues, moved much closer to the EPO approach in the novelty and obviousness assessment.

[109] *See* case T 0939/92 "*Triazole Herbicides/AGREVO*", at para 2.5.4 (cf. section II, C. 1., below) (stating "It follows directly from these considerations that a technical effect which justifies the selection of the claimed compounds must be one which can be fairly assumed to be produced by substantially all the *selected compounds.*"). This general principle is also confirmed in the new 2009 Examination Guidelines for Patent Applications relating to Biotechnological Inventions in the (UK) Intellectual Property Office (UK Biotech Guidelines), para 48, *available at* http://webdb2.patent.gov.uk/biotech.pdf (last visit 10 August 2009) (where it is added with reference to *IG Farbenindustrie AG's Patent* 47 RPC 289, 322-23 (Patent Court):"Furthermore, the advantage provided by the mutation(s) must be in respect of a specific feature of that particular gene, for example a particular sequence involved in a particular function of the corresponding protein.").

[110] *See also* UK Biotech Guidelines, *supra* note 109, at para 48 (considering Lord Hoffman's reference to the EPO Examination Guidelines when regarding the inventive step of an invention that has a number of different components in *Sabaf SpA v MFI Furniture Centres Ltd.* (2005) RPC 10 (House of Lords)).

> individual features. In other words, the interactions of the individual features must produce a synergistic effect. If no such synergistic effect exists, there is no more than a mere aggregation of features (see T 389/86, OJ 3/1988, 87).[111]

Put bluntly, this means that, if each component of the invention interacts with each other and synergy exists between them, then they relate to a single inventive concept having a combined effect. However, if each component forms its own function independently of any of the others then each relates to a separate inventive concept. Yet, for some inventions the synergistic effect might not be evident at first sight.[112] As for microarrays, for example, it appears in accordance with the above mentioned principle that some synergy must be demonstrated between each probe in order for it to belong to the same inventive concept. Moreover, this synergistic use itself would have to be inventive in order for the microarray as a whole to be inventive. This is rather unlikely as each probe in a microarray usually acts independently and therefore no synergy would exist between the probes. This very fact may easily lead to the premature and false conclusion that it would be generally impossible to consider the combined probes on a microarray to belong to the same inventive concept. Yet, it should be understood that if the invention's foundation is in the discovery of a synergistic effect in nature, and the claimed probes can reveal this synergistic effect, then synergy may nevertheless exists.[113] Thus, if specific genes (or proteins) have an important synergistic effect in the development of cancer, then microarray-probes that can be used for the detection of these genes (or proteins) would still relate to a single inventive concept and could therefore be assessed for inventive step as one selection- invention.

6. The mysterious person skilled in the art & common general knowledge

> *The skilled person (or persons) of the EPC is not real, being of average ability for his field but having exhaustive common knowledge and aware of all things that are not technical. He is a legal creation whose purpose is to assist in providing a more objective approach to the assessment of inventive step and other provisions of the EPC. He certainly does not cut an athletic figure, and whilst being able to vault the bar of common knowledge, raising it any higher would be beyond his capability.*[114]

As indicated above, to establish which inventions involve a "reasonable expectation of success" for the "person skilled in the art" and to find out what effects would truly surprise him, it is crucial to consider the EPO's definitions of the capacities and characteristics that such an imaginary person is deemed to have. According to the current EPO Guidelines for

---

[111] *See* EPO Examination Guidelines (2009) at C-IV, 11.5.

[112] As for a more recent decision, *see* case T 1054/05 *"Information management/NEC"* (28 May 2008), headnotes (confirming that the existence of a combination invention requires that the relationship between the features or groups of features be one of functional reciprocity or that they show a combinative effect beyond the sum of their individual effects. The Board found that two features interact synergistically if their functions are inter-related and lead to an additional effect that goes beyond the sum of the effects of each features taken in isolation. It was not enough that the features solve the same technical problem or that their effects are of the same kind and add up to an increased but otherwise unchanged effect).

[113] That national patent offices share this view can be derived from the UK Biotech Guidelines, *supra* note 109 (adding at para. 49, "In such a situation the synergy is not in the probes but in what the probes detect; if there is no synergy in what the probes detect then Sabaf can be applied. For example, if gene X and gene Y were found to have an important synergistic effect in the development of cancer, then probes for the detection of these genes would relate to a single inventive concept according to Sabaf and can therefore be assessed for inventive step as one invention.").

[114] G. Ashley, Member of EPO Technical Board of Appeal 3.2.03, at the 14th European Patent Judges' Symposium, which was held from the 16-20 September 2008 in Bordeaux (France). A written version of his speech is reproduced in the OJ EPO, Spec. ed. 1, 2009, 94-101, *available at* http://archive.epo.org/epo/pubs/oj009/05_09/special_edition_1_judges_symposium.pdf (last visit 10 Sep. 2009).

Examination[115] the "person skilled in the art" should generally be presumed to be an ordinary practitioner aware of what was common general knowledge in the art at the relevant date. "Common general knowledge" can generally be considered to include the information contained in basic handbooks, monographs and textbooks on the subject in question.[116] As an exception, common general knowledge may also include information contained in patent specifications or scientific publications if the invention lies in a field of research that is so new that the relevant technical knowledge is not yet available from textbooks.[117] The person skilled in the art should further be presumed to have had access to everything in the "state of the art", particularly the documents cited in the search report, and to have had at his disposal the normal means and capacity for routine work and experimentation.[118] More specific characteristics and capabilities of the "person skilled in the art" in the biotechnological field are defined in numerous decisions from the EPO Boards of Appeal.

While the skilled person in genetic engineering has been defined as not being as highly qualified as a Nobel Prize laureate,[119] describing the skilled person as a "highly skilled laboratory technician"[120] has been held to be overly restrictive.[121] Rather, he should be assumed to be a scientist or team of scientists working as a teacher or researcher in the laboratories which made the transition from molecular genetics to genetic engineering at the time in question[122]. Yet, the notional skilled person cannot be expected to do any more than carrying out experimental work by routine means within the framework of the normal practice of filling gaps in knowledge by the application of existing knowledge[123].

In particular, it should be empasized that at the EPO a person skilled in the art is not considered to be the same as an inventor. Accordingly, the teaching of a document may have narrower implications for the person skilled in the art than for the inventor.[124] In other words, the mere fact that the inventor applied a certain technology does not necessarily allow the conclusion that, therefore, it was also obvious for the person skilled in the art to try the (combination-) invention with a reasonable expectation of success. The Board of Appeals has specifically held that the person skilled in the art does not possess any inventive capability,

---

[115] Guidelines for Examination in the European Patent Office (April 2009), part C, Chapter IV-22, 11.3.

[116] *Id.* at part C, Chapter II-2, 4.1 (referring to T 171/84 (24 October 1985), OJ 4/1986, 95, para 5 ff.).

[117] *Id.* (referring to T 51/87 (8 December 1988), OJ 3/1991, 177, para 9); *see also* the confirmation of these principles in T 772/89 *"Genomic bovine growth hormone"* (18 October 1991), para 3.3.

[118] *Id.* at part C, Chapter IV-22, 11.3.

[119] Case T 60/89 *"Fusion proteins/HARVARD"* (31 August 1990), OJ EPO 1992, 268, para 2.2.4.

[120] Case T 223/92 *"Human γ-interferon/GENENTECH"* (20 July 1993), at para 5.5. (Bearing in mind that molecular biology is a highly complex technical field in which practicing scientists that plan new projects must have a complex background of knowledge and training, a "highly skilled laboratory technician" is certainly not an appropriate description. In that context it is noteworthy that the Board, probably concerned about its overly restrictive meaning, later reconsidered its unusual definition and issued a correction of this decision.).

[121] *See case* T 412/93 *"Erythropoietin/KIRIN-AMGEN"* (21 November 1994) (where it was concluded in a case related to the production of erythropoietin that the person skilled in the art knows more than opined in T 223/92. Instead this decision provided at para 4 a very precise definition of the person skilled in the art. In particular, the parties agreed that for this particular case "the skilled person should be treated as a team of three, composed of one PhD researcher with several years' experience in the aspect of gene technology or biochemistry under consideration, assisted by two laboratory technicians fully acquainted with the known techniques relevant to that aspect." Moreover, it was agreed that the composition of the team might vary depending on the knowledge and skills required by the particular aspect dealt with.).

[122] Case T 60/89 *"Fusion proteins/HARVARD"* at para 2.2.4.

[123] For more detail, *see* the decisions in Case T 500/91 *"Alpha Interferons/Biogen II "* (21 October 1992), para 2.2; Case T 886/91 *"Hepatitis B virus/BIOGEN"* (16 June 1994); Case T 223/92 *"Human γ-interferon/GENENTECH"* (20 July 1993); Case T 530/95 *"Xma I / NEW ENGLAND BIOLABS"* (10 June 1997); Case T 791/96 *"Pseudorabies/UPJOHN"* (15 November, 1999); and *see also EPO Case Law of the Boards of Appeal* Part I, Chapter D, 7.1.3. (5th ed. 2006).

[124] Case T 5/81 *"Solvay"* (4 March 1982), OJ EPO 1982, 249, para 11.

which is what distinguishes him or her from the inventor,[125] and would not enter into unexplored areas.[126]

Very interesting, when comparing the EPO approach with the statements of the U.S. Supreme Court in KSR, are also the findings of the Board in T 207/94 *"Human beta-interferon/BIOGEN"*. Here the Board held that it had to be assumed in the light of T 500/91 *"Alpha Interferons/Biogen II"* that the average skilled person *would not engage in creative thinking.*[127] Rather, the Board found that he or she could be expected to react in a way common to all skilled persons at any time, namely that an assumption or hypothesis about a possible obstacle to the successful realization of a project must always be based on facts. Thus, an absence of evidence that a given feature might be an obstacle to carrying out an invention would not be taken as an indication that the invention could or could not be achieved.[128] While the knowledge of the notional person skilled in the art, according to the Board, must be considered as that of a team of appropriate specialists who knew all the difficulties still to be expected when considering the cloning of a new gene, the Board further held that the skilled person nevertheless must be assumed to lack the inventive imagination to solve problems for which routine methods of solution did not already exist.[129]

In T 455/91 *"Expression of polypeptides in yeast/GENENTECH"* the Board set out more detailed considerations on the skilled person's likely attitude to possible changes, modifications or adjustments in known products or procedures.[130] Its aim was to answer objectively, and avoiding any *ex post facto* analysis, the question of whether it would be obvious to the skilled person to make given changes in a structure or procedure. The Board found that the skilled person in this field was well aware that even a small structural change in a product (e.g. a vector, protein, or DNA sequence) or procedure (e.g. a purification process) could produce dramatic functional changes. Therefore, he would adopt a conservative attitude. However, the Board also clarified that this must *not* be associated with being reluctant or opposed to modify or adjust a known product or process, but rather in the sense of being cautious.[131] For example, the person skilled in the art would neither go against an established prejudice, nor venture into sacrosanct or unpredictable areas, nor take incalculable risks.[132] Yet, within the normal design procedures, he would readily seek appropriate and manifest changes, modifications or adjustments involving little trouble or work and no or only calculable risks, especially to obtain a handier or more convenient product or to simplify a procedure. In particular, the Board also held that the skilled person working in one field of genetic engineering would additionally regard a means conveniently adopted in a neighboring field of genetic engineering as readily usable also in his own field, *if* this transfer of knowledge appears to be easy and to involve no inventive skills or obvious risks.[133]

---

[125] Case T 39/93 *"Polymer powders/ALLIED COLLOIDS LIMITED"* (14 Febr. 1996) , para 7.8.4. .

[126] *See case* T 500/91 *"Alpha Interferons/Biogen II"* (21 October 1992), para 2.2 (where it was also held the person skilled in the art cannot be expected to perform scientific research in areas not yet explored).

[127] Case T 207/94 *"Human beta-interferon/BIOGEN"* (8 April 1997), para 34, with reference to Case T 500/91 *"Alpha Interferons/Biogen II"* (21 October 1992).

[128] *Id.*

[129] Case T 223/92 *"HIF-Gamma/GENENTECH"* (20 July 1993), para 5.5 (when considering the notional skilled person in genetic engineering as of October 1981, i.e. more than one year later than in T 500/91. By this time, much more genes had been cloned and expressed, and the skills in this technical field were developing rapidly.).

[130] *See* case T 455/91 *"Expression of polypeptides in yeast/GENENTECH"* (20 June 1994), 1995 OJ 684.

[131] *Id.* at para 5.1.1.3. (describing the person skilled in the art as a rather hesitant person).

[132] *Id.*

[133] *Id.* at the headnote. *See also* case T 1102/00 *"Mammalian membrane receptors/CNRS"* (1 June 2004), para 14 (where it was held with reference to T 455/91that the skilled person working in a certain field does not remain inactive, but always seeks alternatives or changes in known processes or/and products when little work and no risks are involved using routine measures and without applying inventive skills).

In T 387/94 *"Chimeric genes/MONSANTO"* the Board further emphasized that the neighboring area must be very close.[134] Case law has also established that, if the problem prompts the person skilled in the art to seek its solution in another technical field, the specialist in that field is the person qualified to solve the problem. The assessment of whether the solution involves an inventive step must therefore be based on that specialist's knowledge and ability[135] and might thus involve a team of specialized scientists.[136] For instance, if the closest prior art is in the protein field and the problem to be solved is to clone the DNA encoding this protein, the person skilled in the art is in the field of biotechnology and must be seen as a team comprising specialists in carrying out rDNA experiments.[137] On the other hand, if he would expect to have to perform scientific research rather than routine work in order to transfer a technology previously set up in one field of research to a neighboring field then inventive step could be acknowledged.[138]

In summary, even though the numerous decisions described above provide rather detailed guidelines on the specific character and the capacity of the person skilled in the art, a lot will still depend on the specific field in which the invention is made and on the particular circumstances of each case. Moreover, it can be presumed that as technology and knowledge develops the average person skilled in the art will inevitably become an ever more sophisticated scientist. As a result the person skilled in the art remains a rather mysterious figure. For the time being, the probably most appropriate summary of the present case law was formulated by *Hans-Rainer Jaenichen*, who considered it feasible to define the person skilled in the art in the area of biotechnology as:

> "a team of cautious PhD. bench molecular biologists including laboratory assistants that is capable of practically applying methods known in the art, that is aware of the disclosure of pertinent prior art documents, and that has the necessary manual dexterity and lack of fatigue."[139]

Whilst this seems to be a quite accurate description, it should perhaps be added that the Board has indicated in a more recent decision that it would further consider the neither-particularly-creative-nor-innovative person skilled in the art to have a global view when dealing with a particular problem. In T 493/01 *"Acellular vaccine/CELLTECH,"* the invention related to a protective antigen potentially useful in a vaccine against whooping cough. Referring to the aforementioned decision in T 455/91, where the skilled person in the field of biotechnology was already described as being cautious and conservative, the Board held that this did not mean he would refrain from considering information because it did not concern the mainstream of research in his field of specialization or because it only applied to some parts of the world. His skill and knowledge would not be geographically limited and he would in fact have had a global point of view.[140] Considering these findings in light of the increasing globalization and sophistication of scientific endeavors, it will be utterly import

---

[134] *See* case T 387/94 *"Chimeric genes/MONSANTO"* (7 March 1997), para 35.

[135] *See* Guidelines for Examination in the European Patent Office (April 2009), part C, Chapter IV-22/23, 11.3., (referring to Case T 32/81 *"Fives-Cail Babcock"* (5 March 1982), OJ 6/1982, 225, in the the headnotes.

[136] *Id.* (adding that there may be instances where it is more appropriate to think in terms of a group of persons, e.g. a research or production team, than a single person. This may apply, for example, in certain advanced technologies (...) and in highly specialised processes such as the commercial production (...) of complex chemical substances.); *see also* case T 500/91, *supra* note 123, para 2.2; *cf.* T 141 /87; T 60/89.

[137] *See* case T 29/99 *"Serine protease inhibitors/AMGEN"* (6 February 2002), para. 7.

[138] *See* case T 441/93 *"Cloning in Kluyveromyces/GIST BROCADES"* (27 March 1996), in the headnotes.

[139] *See* Jaenichen et al., *supra* note 71, at para 3.1.1. *Cf.* case T 412/93 *"Erythropoietin/KIRIN-AMGEN"* (21 November, 1994) (where it was concluded at para 4 that the notional skilled person can then be treated as comprising a PhD. Researcher and two laboratory assistants having the necessary manual dexterity and lack of fatigue).

[140] Case T 493/01 *"Acellular vaccine/CELLTECH"* (4 June 2003), para 7 (concluding that if a pathogen constituted a known threat in some restricted parts of the world, the skilled person would not refrain from taking prior art knowledge about that pathogen into consideration or from using it as basis for his activities).

for biopharmaceutical companies to closely follow how the the EPO's definition of the person skilled in the art will develop in the near future.[141]

B. Selected DNA and protein- related case law from the EPO

The following section briefly demonstrates how the EPO applies the above described general principles for the assessment of inventive step more specifically in additional selected cases dealing with DNA and its expression products.[142]

1. Basic test: Difficulties in the isolation procedure or in the identification of uses

Many cases relating to nucleic acid molecules and their expression products show that the Technical Board of Appeal regularly found an inventive step when there was evidence of *particular difficulties in the isolation procedures.* In T 223/92 *"Human γ-Interferon/GENENTECH"* the TBA explains its approach as follows:

> *The goal of the Respondent can be likened to wanting to reach the peak of a mountain which is permanently covered by cloud so that the correct approach route cannot be seen. Whilst it cannot be said with certainty that the differences in the route chosen by the Respondents over known routes where decisive, the Respondents successfully reached this peak, not knowing when they started to climb whether known and as yet unknown difficulties on their chose route might not force them to give up or try some other route. By identifying the DNA sequence, the Respondents so to speak provided a guide rope to the peak which enabled others to be certain of getting to the same peak which much less trouble.*[143]

This so-called "rope to the peak" consideration has been used by the TBA in many cases to support its decision. At least in the early stages of the technology, one could think of a great variety of difficulties that might have arisen in the isolation procedure of DNA and proteins with specific functions. Accordingly, a range of different arguments relating to problems reported in the prior art provided good arguments against a reasonable expectation of success and convinced the Board to regard a DNA sequence as being non-obvious.

For example, in T 637/97 *"Binding protein/GENENTECH"* the *lack of availability of suitable probes* was the reason for the Board acknowledging an inventive step for an

---

[141] For a more detailed recent discussion of *inter alia* the person skilled in the art and the definition of a scientific team at the EPO, see Ingwer Koch, *Das Merkmal der erfinderischen Tätigkeit als Korrektiv des Patenrechts*, GRUR Int. 2008, Heft 8-9, 669, 674 ff. (in German) (arguing against the establishment of a statutory definition of the person skilled in the art). Interestingly, the various definitions of the person skilled in the art in the national system and at the EPO were also the topic of a working session at the 14th European Patent Judges' Symposium. A written version of the speeches held by the patent judges Sir Robin Jacob (UK), Bernard Corboz (Switzerland) and Graham Ashley (EPO) is provided at pp. 83-101 in the OJ-EPO, Special edition 1, 2009, *supra* note 114. (See in particular, G. Ashley, who, addressing "the raising of the bar" issue and the fact that a change in the definition of the skilled person is currently being considered, states at p.101: "However, as can be seen from the above, the skilled person is a very different person (or persons) depending upon the technical subject-matter under consideration, which makes the provision of a standard definition very difficult. In addition, raising the level of skill of the skilled person would have an effect not just on inventive step, but also on sufficiency of disclosure and clarity, and in these cases, the consequence would be a "lowering of the bar" for these requirements. The concept of the skilled person is thus an inappropriate means for increasing the level of inventive step.").

[142] More generally, it is noteworthy that EPO case law has established that recombinant proteins can derive their inventive step from the inventive step required for providing the DNA sequences encoding them, *see* case T 412/93 *"Erythropoietin/KIRIN-AMGEN"*. Moreover, surprising properties or inventive effort in providing a complete and biologically active protein from natural sources can also support inventive step; for further specific case law on proteins and monoclonal antibodies, cf. Jaenichen et al., *supra* note 71 at para 17.1.7. ff.

[143] Case T 223/92 *"Human γ-Interferon/GENENTECH"* (20 July 1993), para 5.15.

invention directed to a DNA molecule encoding the insulin-like growth factor binding protein, BP53.[144] The prior art disclosed SDS-PAGE electrophoresis of BP53 and sequencing of fifteen amino acids at the amino terminus.[145] The Board held that the skilled person would not have had a good starting point for making suitable probes for screening DNA libraries for a BP53 DNA based on the work on other genes because of the unique characteristics of each gene.[146] The sequence of fifteen amino acids was useless for designing probes due to its high level of degeneracy. Hence, the skilled person would not have had *a reasonable expectation of success* in isolating a DNA molecule encoding BP53,[147] and the Board concluded that the claimed invention satisfied the inventive step requirement.[148]

In the more recent case T 759/03 *"FIV/St. Vincent's Institute, et al."*,[149] the invention related to the detection of feline immunodeficiency viruses. The priority date was 14 June 1991. The problem to be solved in light of the prior art was the provision of a peptide consisting of an immunodominant region of FIV useful for the detection of FIV having greater specificity and sensitivity, compared to available assays known in the art. The respondent/patent proprietor argued that epitope-mapping at the relevant date, more than fifteen years ago, was a complex and difficult task. The Board agreed and found that:

> ...in a quickly developing technical field a method, which today belongs to the everyday routine job of a skilled person, fifteen years ago might have been uncertain and highly complex. However, in spite of the understandable uncertainties which always characterise experiments using biological compounds like proteins and antibodies, it had to be asked whether the skilled person at the relevant date of the patent had reason to adopt a sceptical attitude or if he/she would have had either some "expectations of success" or, at worst, no particular expectations of any sort, but only a "try and see" attitude, which – as pointed out in decisions T 333/97 of 5 October 2000; point (13) of the reasons - does not equate with the absence of a reasonable expectation of success (T cf. decision T 1045/98 of 22 October 2001; point (17) of the reasons).[150]

Then, however, the Board stated that it could not be concluded from any of the documents cited, including post published documents, that a skilled person, having adopted the "try and see" attitude would have succeeded in providing the aforementioned peptide in claim 1.[151] Therefore, the Board concluded that the skilled person would not have arrived at the claimed invention in an obvious way and the inventive step was acknowledged in accordance with article 56 EPC.[152]

Subsequently, the Board reached a similar conclusion in T 1599/06 *"Mycobacterium vaccinating agent/UNIVERSITY OF CALIFORNIA"*,[153] which further defined the limits for

---

[144] Case T 637/97 *"Binding protein/GENENTECH"* (17. October 2000). *See also* case T 530 /95 *"Xma I/NEW WNGLAND BIOLABS"* (10 June 1997) (concerning problems reported in the prior art for a certain cloning approach); and case T 425/96 *"Tomato plants/MONSANTO"* (20 September 1999) (concerning problems for the expression of a particular DNA sequence in a transgenic plant).

[145] *Id.* at paras. 6-7.

[146] *Id.* at paras 8-9.

[147] *Id.* at para 9.

[148] *Id.* at para 11.

[149] Case T 759/03 *"FIV/St. Vincent's Institute, et al."* (17 August 2006).

[150] *Id.* at para 36.

[151] *Id.* at para 37.

[152] *Id.* at para 38. As for another recent case where inventive step was acknowledged *see case* T 1165/06, *"Schering/ IL-17 related polypeptide"* (19 July 2007), where the lack of significant homology between the IL-174 gene and other known IL-17 family members meant that a reasonable expectation of success of retrieving that gene could not be assumed when screening DNA libraries with routine techniques. In other words, it would not be obvious to look for the IL-174 gene, nor would routine screening techniques have been sufficient to identify the gene.

[153] Case T 1599/06 *"Mycobacterium vaccinating agent/UNIVERSITY OF CALIFORNIA"* (13 September 2007).

the applicability of the "try and see" notion to support rejection under article 56 EPC. The case concerned a patent application relating to vaccines against Mycobacterium tuberculosis. The application comprised *inter alia* claims on specific proteins with special immunoprotective functions, which hade been rejected by the Examining Division. Among other things the examiner had argued that by applying previously known methods the skilled person would only have had to adopt a "try and see" approach to inevitably identify all proteins of the fraction with an immunoprotective function.[154] Considering this argument the Board stated:

> There have been cases where inventive step was denied by the boards of appeal because the skilled person was in a "try and see" situation. Such a situation was considered to have occurred if the skilled person, in view of the teaching in the prior art, had already clearly envisaged a group of compounds or a compound and then determined by routine tests whether such compound/s had the desired effect (T 91/98 of 29 May 2001, points 7 and 8 of the reasons; T 889/02 of 22 March 2005, point 7 of the reasons; T 542/03 of 14 July 2005, point 14 of the reasons; T 1241/03 of 1 September 2005, point 31 of the reasons).[155]

In the case at hand, however, the skilled person was, in the view of the Board, not in a "try and see" situation because nothing in the prior art documents pointed to the claimed protein as a possible agent for inducing a protective immune response.[156] After rejecting further arguments of the Examining Division, which asserted that the uses for the claimed proteins were predictable due to their known immunological properties and thus obvious,[157] the Board remitted the case to the department of first instance with the order to grant a patent.

On the contrary, in a line of early cases, the Board already failed to find an inventive step when the methods of isolation were well established *and* the outcomes were predictable at the time the invention was achieved. T 386/94 *"Chymosin/UNILEVER"* was one of the earlier EPO decisions[158] where the Board explicitly denied inventive step for particular

---

[154] *Id.* at para 20.1.

[155] *Id.* at para 20.2.

[156] *Id.* at para 20.2 (referring to the content of the documents mentioned in paras 21-21.7).

[157] *Id.* at para 21-21.8 (in doing so the Board, first considered the appellant's counter-argument that a person skilled in the art had no guarantee of knowing whether any of the proteins could provide protective immunity. In that regard, the Board referred to prior case law which had established that subject-matter is obvious not only when results are clearly predictable, i.e. when it is certain that a result will be achieved, but also when there is a reasonable expectation of success (for example T 1241/03 of 1 September 2005). Therefore, the Board rejected this argument. However, then the Board continued by holding that evaluating the "reasonable expectation of success" involves analyzing the prior art to determine the degree of confidence it gives the skilled person that an envisaged result will be obtained. If that degree of confidence is too low, the reasonable expectation turns into a mere hope to succeed. According to the Board a skilled person working on that basis follows a non-obvious course of action. For the Board, the evidence cited in this case indicated that at the priority date the skilled person generally could not make any reliable rational predictions about the likelihood of obtaining protective immunity with an antigen even if it elicited a cell-mediated immune response. In addition, there was no evidence on which it could be established that Mycobacterium tuberculosis was an exception from that general rule. Thus the court concluded, that the skilled person would not have used the subject-matter of claim 1 with a reasonable expectation of success. Therefore, it was held to be non-obvious.).

[158] Compare also Genentech Inc.'s Patent, (1989) R.P.C. 147 (Eng. C. A. 1988). It is one of the earliest European inventive step rejections by a national court involving an invention directed to isolated DNA molecules encoding human tissue plasminogen activator ("t-PA"). The court held that it was obvious to the person skilled in the art to produce human t-PA by recombinant DNA technology. Oligonucleotide probing was a known technique, and the skilled worker would have arrived at the claimed invention because the choice of oligonucleotide probes did not require skill and experience of a high order. In fact, all the teams that set out to produce human t-PA by recombinant DNA technology succeeded. The court reasoned that the monopoly that would be granted to the inventors by a patent far outstrips any legitimate reward for their success in winning the race to recombinant expression of the gene, and hence the claimed invention failed for want of an inventive step. In the decision, the Court focused on the obviousness of the methods of isolating the DNA molecules, rather

claims on DNA molecules as such due to routine isolation methods.[159] In this case, the Board considered claims to DNA molecules encoding preprochymosin as well as its mature form. The prior art disclosed that chymosin is a milk clotting protein that has a precursor protein of 365 amino acids. The prior art also taught the isolation of a clone comprising 80% of the prochymosin molecule.[160] As for the main request, the Board held that the person skilled in the art would be reasonably confident that, based on the prior art and the standard knowledge, one could successfully clone the DNA molecules encoding preprochymosin as well as its mature form. Hence, the Board found a *"reasonable expectation of success"* in light of the prior state of the art and that the claimed invention, therefore, lacked an inventive step.[161] In reaching its conclusion the Board explicitly differentiated the level of the prior art and the factual circumstances in the case at hand from the situations in its previous decisions, thus confirming the significance of a thorough case-by-case assessment. The Board concluded:

> 45. This decision is not in contradiction with other appeal decisions in some cases of the same time period, which acknowledged the cloning of other specific cDNA molecules as involving an inventive step (T 923/92, (tissue plasminogen activator), (OJ EPO 1996, 564, T 412/93 (erythropoietin) dated 21 November 1994, T 223/92 (IFN-gamma) dated 20 July 1993 and T 128/92 dated 30 November 1994, (interleukin-II), all not published in OJ EPO). 46. In all of these earlier cases, however, it was concluded by the competent boards of appeal that the isolation of the cDNAs would only be successful if one or more of the difficulties enumerated in point 36 supra could be solved. In each case, the mRNA was present in low abundance and the sequence of the protein to be expressed was either unknown or ambiguous. In the case of tissue plasminogen activator, the mRNA was, moreover, of a very large size. As for erythropoietin, no reliable source of mRNA was available. 47. Thus, the present decision is an illustration of the general principle expressed in particular in decision T 158/91 (supra) that each case must be assessed on its own merits.[162]

The Board reached a similar conclusion in T 475/93 *"IGF-II/CHIRON"*, where the claimed invention was directed to a DNA molecule encoding human insulin-like growth factor ("IGF") II having a particular sequence.[163] Here, the prior art disclosed proteins belonging to the IGF family and suggested that the amino acid sequences of IGF-I and IGF-II could be used to determine oligonucleotides for use in screening for DNA molecules.[164] The prior art also taught a cDNA library from liver.[165] The Board held that the skilled person would have expected to successfully isolate an IGF-II DNA molecule by probing the liver cDNA library, since the liver was known to be the site of production of IGF-II. Hence the claimed subject matter did not involve an inventive step.[166]

In the more recent decision in T 1396/06 *"HLA binding peptides / EPIMMUNE"*,[167] the Board did not find an inventive step although the applicant had spent considerable efforts to arrive at the invention. As the applicant had only followed routine methods he was

---

than on the structural obviousness of the DNA molecules as in the US, and the court was greatly concerned about giving away patent rights based on the speed of performing the methods rather than based on ingenuity.

[159] Case T 386/94 *"Chymosin/UNILEVER"* (11 January 1996); *cf. supra* note 68. *See also* case T 886/91, *"Hepatitis B virus/BIOGEN"* (16 Juni 1994) at para 8.2.4 & case T 495/92, *"Gln9-interferon variant/CANCER INSTITUTE"* (19 September 1995) at paras 6-8 (both T 886/91 and T 495/92 indicated that as all the necessary methods and means as well as techniques for the location of the DNA sequence analysis were known in the art, only surprising properties could form the basis for an inventive step).

[160] *Id.* at para 25.

[161] *Id.* at para 44.

[162] *Id.* at para 45-47.

[163] Case T 475/93 "*IGF-II/CHIRON*" (17 July 1997).

[164] *Id.* at para 3-4.

[165] *Id.* at para 11.

[166] *Id.* at paras 25-26.

[167] Case T 1396/06 "*HLA Binding Peptides/EPIMMUNE*" (31 May 2007).

considered to have been in a "try and see" situation. The ruling concerned an appeal from a decision of the Examining Division rejecting the appellant's application for lack of inventive step. The invention concerned immunogenic peptides of particular amino acid sequences, compositions containing the same, and use of the peptides in medicine including, in particular, the treatment of HIV infection. The Board upheld the Examining Division's decision that the claims of the appellant's main request, as well as the claims of the first to fifth auxiliary requests lacked inventive step. Regarding the main request, the Board decided that even though the appellant's evidence suggested that the work resulting in the provision of the claimed peptides would require considerable time and effort, the procedure only involved methods which fell within the normal routine capacity of the average person skilled in the art.[168] Although accepting that a skilled person, even when applying the routine methods with the aim to solve a closely related technical problem, would not have absolute certainty to succeed, the Board then referred to its previous case law and emphasized that "certainty of success" was not required and that a claim may lack inventive step if the skilled addressee would arrive at the solution to the problem *merely* by following a "try it and see" approach.[169] Considering the facts of the case, the Board further held that a combination of two prior art documents was sufficient to direct the skilled addressee to arrive at the solution underlying the problem, i.e. the provision of peptides specifically binding to a particular HLA-allele. Therefore, the Board was convinced that a skilled person would arrive at the invention according to the main request in an obvious way.[170] Consequently the main request was rejected for lack of inventive step. However, asdiscussed further below in Part II. C. 3, the Board reached a different conclusion when considering the inventiveness of the *sixth auxiliary request*, in which ten claims were restricted to an immunogenic peptide *consisting of* one specific amino acid sequence with specific properties that suggested its use in HIV treatment.

More generally, not only T 386/94, T 475/93 and T 1396, but also T 759/03 (albeit with a different result) illustrate that today the EPO will regularly not consider the mere isolation of a gene sequence to be inventive. Instead, the EPO will usually require specific evidence of truly surprising properties or functions.[171] This trend becomes even more evident when taking a closer look at case law relating to gene homologies.

2. Specific case law relating to homologies in different organisms

Whenever inventive step has to be assessed in the biotechnological arts, it has become increasingly common that there exists a homologue sequence to a claimed gene or protein

[168] *Id.* at para 6.

[169] *Id.* at para 7 (holding: "However, certainty of success is not required according to the jurisprudence of the Boards of Appeal, which makes a clear distinction between reasonable expectation of success and certainty of success (cf. decision T 918/01 of 6 October 2004, point (9.1) of the reasons). Rather, in spite of the understandable uncertainties which always characterize biological experiments, the skilled person would have had no reasons to adopt a sceptical attitude. He would have had either some expectations of success or, at worst, no particular expectations of any sort, but only a "try and see" attitude, which does not equate with an absence of a reasonable expectation of success (cf. decision T 91/98 of 29 May 2001, point (8) of the reasons for the decision and decision T 1045/98 of 22 October 2001; point (17) of the reasons for the decision.").

[170] *Id.* at para 8.

[171] That this development was already evident at the turn of the millennium is demonstrated by Alexander Richard Krefft, *Patente auf human-genomische Erfindungen*, Schriftenreihe des Max Planck Instituts zum gewerblichen Rechtsschutz, Band 122 (Heymanns 2003) (in German), 154 – 155 (with further references).

sequence which has already been disclosed in the prior art.[172] Often researchers discover that a specific human gene and the protein it is coding for have a particular function that can be utilized through the claimed invention in their patent application. Yet, during the examination procedure it is revealed that a corresponding gene or protein with the same or similar function is already known for another living organism, for example a pig, mouse or rat. In many cases, precisely this homologue was utilized by the researchers in order to isolate annotate the corresponding human gene. At least in the early days of gene technology, applicants who had utilized known homologues to arrive at their asserted invention still had a considerable chance to convince the Board that their patent claims involved an inventive step due to the relatively undeveloped, unpredictable prior art and the immature common general knowledge.

For example, in T 236/96 "*Interleukin 1/DAINIPPON*" the Board considered claims to a DNA comprising a coding sequence for the precursor to human IL-1.[173] Although the prior art disclosed at the relevant priority date for the claims (ranging from1984-1985) cloning of a murine IL-1 cDNA, the prior art also disclosed significant differences between human and murine IL-1.[174] For this reason, the Board held that the skilled person would not have had *a reasonable expectation* that the human and murine DNAs were so homologous that one could be used to probe for the other. Therefore the cloning of human IL-1 DNA was inventive.[175]

The Board arrived at a similar decision in T 280/00 *"Inhibin/GENENTECH"*.[176] This case related to an appeal concerning the amendments of a patent with various priority dates in the designated countries ranging from 1985 to the year 1986. The patent claimed human DNA sequence coding for the hormone inhibin, which is a specific hormone that down regulates synthesis and inhibits the secretion of the follicle-stimulating hormone FSH. Considering the state of the prior art the Board found that information on successfully isolated bovine and porcine inhibin was already available. Moreover, cDNA coding for inhibin in porcines had been previously isolated. Starting from the closest prior art, the technical problem to be solved was defined by the Board to lie in the provision of a further (human) inhibin molecule. The claimed invention purported to solve this problem by cloning and expressing the DNA sequence encoding the human inhibin chains. The Board further stated that the knowledge about the function of bovine and porcine inhibin suggested that inhibin was a particularly interesting substance from a medical perspective. Thus, in the Board's judgment, the skilled person seeking to solve the above mentioned problem would have thought that human inhibin was a particularly desirable protein to produce if only for its therapeutic potential. However, at the same time, the Board acknowledged that ever since the postulation of the existence of inhibin, the protein *per se* has always been an elusive protein.[177] Considering the decisive question of whether a "reasonable expectation of success" existed, in light of the prior art, for arriving at the claimed invention by following the route chosen by the applicant, the Board particularly emphasized that by using a probe made from the knowledge of the porcine inhibin amino acid sequence in order to isolate human inhibin (cross-species hybridization), the applicant had chosen a route that significantly departed from the teachings in the prior art. The prior art would instead have directed the skilled person to first attempt to isolate a partially human inhibin as a first step to

[172] Due to increasingly effective mass sequencing methods and a growing number of easily accessible high quality gene- and protein-libraries and -banks.
[173] Case T 236/96 "*Interleukin 1/DAINIPPON*" (13 April 1999).
[174] *Id.* at 18.
[175] *Id.* at 19.
[176] Case T 280/00 *"Inhibin/GENENTECH"* (6 February 2003).
[177] *Id.* at para 18.

the cloning procedure.[178] Although the Board accepted that the hypothetical homology indicated in the prior art might have given the skilled person some hope that he/she might succeed in isolating the gene by cross-species hybridization,[179] the Board nevertheless decided that this hope did not amount to a "reasonable expectation of success". In arriving at this conclusion, the Board referred to the absence of any indication/suggestion in the prior art that some degree of homology could be expected to exist between the human inhibin gene to be cloned and its presumed already known counterpart in another species.[180] For these reasons, the Board acknowledged an inventive step for both the claimed human gene and the human inhibin chains that it encoded.

In that context it should, however, be noted that T 236/96 *"Interleukin 1/DAINIPPON"*, and even T 280/00 *"Inhibin/GENENTECH"* concerned patent applications with priority dates from the mid/late 1980's, i.e. from a time when the common general knowledge and the prior art was not particularly advanced. In more recent decisions concerning similar claims filed from the mid/late 1990's, the Board usually arrived at different inventive step- conclusions. For example, in T 111/00 *"Monokine/FARBER"*, the claimed invention was directed to a DNA molecule encoding a mammalian monokine induced by gamma interferon ("MIG") with at least 90% identity to particular nucleic acid sequence.[181] The prior art disclosed an isolated mouse DNA molecule encoding cytokine induced by interferon. The disclosed DNA molecule had 78% identity to the particular nucleic acid sequence claimed, and the prior art suggested studying the wide involvement of such macrophage products because of the involvement of macrophages in human health and disease. Since the high therapeutic potential of human cytokines was well established and no human homologue to the newly isolated cytokine was to be found among the already known human cytokines, the Board found that the skilled person would have had a clear incentive to look for this human homologue.[182] The Board also reasoned that isolation of the human cytokine cDNA was carried out in a straightforward manner using the prior art DNA as a probe, and the skilled person would have considered cloning of the human cDNA as a matter of routine experimentation since the probe was available and no problems were encountered. Under these circumstances the Board particularly did *not* regard the approach of a "reasonable expectation of success" to be applicable, which had been developed to address the unpredictability of complex technologies. Therefore, the Board decided that neither the claimed human cDNA nor the encoded cytokines could derive inventive step from the way they were isolated.[183] Finally, the Board held that *no* evidence had been submitted which would allow to conclude that the claimed human gene had unexpected properties in comparison to the corresponding mouse gene.[184] Consequently inventive step was denied.

The Board had to address a similar situation in T 0150/03 *"Channel proteins/CHIBA UNIVERSITY"*[185]. The claimed invention at issue was directed to specific human channel proteins and the human cDNA that encoded them. However, both homologues cDNA from rats, as well as the encoded rat channel proteins were previously known. Moreover, the

---

[178] *Id.* at 21.
[179] *Id.* at 22 (the prior art mentioned that bovine and porcine inhibins show some similarity at the amino acid sequence level and underlines the similarity between porcine inhibin, and human and mouse TGF-α, also at the amino acid sequence level, thus drawing attention to the homology which sometimes exists between proteins of various mammals and, possibly, between the corresponding encoding DNAs).
[180] *Id.* at para 22.
[181] Case T 111/00 "*Monokine/FARBER*" (14 February 2002).
[182] *Id.* at para 2 - 5.
[183] *Id.* at para 5 – 7 (concluding that in the present case, the skilled person would have considered the cloning of human cDNA as a matter).
[184] *Id.*, para 9.
[185] Case T 0150/03 "*Channel proteins/CHIBA UNIVERSITY*" (25 June 2004).

background art had already either indicated the existence of a human protein closely related (with more than 92% amino acid sequence identity) to the rat protein or suggested the development of functional human homologues.[186] Under these circumstances the Board held that the prior common general knowledge provided a strong incentive for the skilled person to try to find human homologues. In light of the high sequence identity and the advanced common general knowledge, the Board further found that the skilled person would have been in the position to easily retrieve from a gene bank all the necessary information about the DNA sequence encoding the rat channel protein. Using this information, the skilled person could have easily prepared a cDNA fragment to be used as a probe to screen a human cDNA library and to identify a cDNA encoding a human homolog of the rat channel protein.[187] Thus, the Board held that he/she would have had a "reasonable expectation of success" to find the human channel protein and the gene encoding it. Consequently, the patent application was rejected for lack of inventive step under article 56 EPC.

Considering the rapid technological and scientific development during the recent years, it can therefore be concluded, that the Board will nowadays regularly regard the mere isolation of polynucleotides and (corresponding) polypeptides through simple homology comparison, as well as the identification of their function(s) with the help of known sequence homologues from different organisms, to be a routine, non-inventive and thus obvious procedure.[188] Although each case should still be examined on its own merits, it is reasonable presume that any different results, like e.g. in T 236/96 and T 280/00, will most likely become the exception in an age of increasingly effective bioinformatics tools and data mining. Yet, in the growing number of cases where the starting materials are available and the isolation of a sequence is routine, secondary indicia, such as unexpected properties, may still render the claimed sequence inventive. Then, however, it will be important to demonstrate that a particular property is truly surprising in comparison to the already disclosed function of a formerly known homologue.

3. Further case law on secondary indicia in biotechnology

As indicated above, in a growing number of cases, the EPO will have to turn to secondary indicia in its inventive step assessment of DNA and protein-related inventions. In this specific field of research, it is particularly secondary evidence relating to surprising properties that appears to have become increasingly significant for the success of today's patent applications. The question is then: What exactly will be regarded as such surprising properties? In that context it should first be noted that in most cases not the direct properties of the novel DNA in question are examined, but rather the qualities of the novel protein that is encoded by that DNA.[189]

One relevant decision is T 182/03 *"Phosphodiesterase/SMITHKLINE BEECHAM."*[190] The case related to a previously rejected patent application claiming *inter alia* a gene

[186] *Id.* at paras 2-5.
[187] *Id.* at paras 10-12.
[188] This also seems to be the case for gene identifications in a database with the help of known structural information about the corresponding protein. For further explanations see part II and cf. e.g. the most recent *Examination Guidelines for Patent Applications relating to Biotechnological Inventions in the (UK) Intellectual Property Office UK* (April 2009), para 34, *available at* http://webdb2.patent.gov.uk/biotech.pdf (last visit: 10 June 2009) (referring to EPO and UK case law, as well as to new techniques, new bioinformatics tools and data mining procedures).
[189] Peter Rauh & Hans-Rainer Jaenichen, *Neuheit und erfinderische Tätigkeit bei Erfindungen, deren Gegenstand Proteine oder DNA-Sequenzen sind,* 11 GRUR, 753, 757 (1987).
[190] Case T 182/03 *"Phosphodiesterase/SMITHKLINE BEECHAM"* (23 June 2004).

sequence (isolated from human brain tissue) coding for a particular form of cAMP[191]-specific phosphodiesterase (cAMP PDE). This is an enzyme that affects cAMP-dependent cell signaling pathways. These pathways play a key role in many diseases, such as depression. Thus the regulation of cAMP depending pathways with the help of phosphodiesterase was believed to be of great significance in developing potential treatments against such diseases. Considering the facts of the case, the Board emphasized that several documents in the prior art already disclosed non-human and one human cDNA coding for other forms of cAMP PDE than that claimed in the patent application.[192] However, the prior art also indicated difficulties in utilizing the disclosed cDNA sequence for identifying/developing potential drug candidates. This was due to the existence of a great number of different variations of cAMP PDE. Moreover, it was pointed out in the prior art that cAMP PDE is expressed in many different types of tissue and that further studies would have to be conducted to obtain more information about its various splicing forms, their effects, and its great pharmacological potential.[193] Under these circumstances, the Board found that a person skilled in the art was on the basis of the prior knowledge not in a position to decide how many different variations of (human) cAMP PDE existed.[194] Consequently the Board rejected the applicants argument that that the formulation of the problem, i.e. to isolate an alternative cAMP PDE encoding DNA, was *per se* inventive, either because the skilled person would understand from the prior art that the genomic gene corresponding to the cDNA already isolated was probably the only human cAMP PDE encoding gene, or because all such human genes had already been cloned from brain tissue.[195] Furthermore, the appellants did not challenge the Board's conclusion that at the priority date, the cloning of cAMP-specific phosphodiesterase cDNAs could be done as a matter of routine.[196] Thus, the remaining question was whether this would have led the skilled person in a straightforward manner to the particular sequence which is claimed. Addressing this final argument in support of an inventive step the Board held:

> Under these circumstances, inventive step could nevertheless be acknowledged on the basis of unexpected findings or properties regarding/characterising the specifically claimed cDNA or the corresponding protein. The Appellant argued (see point IV supra) that the claimed cDNA encoded a cAMP PDE with unexpected properties, it being structurally divergent from other PDEs and its expression being restricted to specific tissues. It was pointed out that these properties made it particularly suitable for drug targeting and that a drug had de facto been developed using the enzyme as a target. The Board is not aware of any data refuting these arguments. They, in turn, warrant acknowledgement of inventive step irrespective of whether document (E19) or document (D1) is taken as closest prior art.[197]

For this reason the Board finally concluded that the requirements of Article 56 EPC were nevertheless fulfilled.[198]

---

[191] Cyclic adenosine monophosphate (cAMP,) is a second messenger that is important in many biological processes. cAMP is derived from adenosine triphosphate (ATP) and used for intracellular signal transduction in many different organisms, conveying the cAMP dependent pathway. In humans, cAMP and its associated kinases function in several biochemical processes, incl. the regulation of glycogen, sugar, and lipid metabolism.

[192] Case T 182/03 "*Phosphodiesterase/SMITHKLINE BEECHAM*" at paras 2-4.

[193] *Id.* at para 6 ff.

[194] *Id.* at para 9.

[195] *Id.* at paras 8-10.

[196] *Id.* at para 11.

[197] *Id.*at para 12.

[198] *Id.* (Of note: A very early example of this approach could already be found in case T 301/87, *BIOGEN/Alpha-interferon* (16 February 1989). In this case the Board held that claims directed to recombinant DNA molecules comprising specific deposited DNA inserts encoding IFN-alpha satisfied the inventive step requirement. Although the prior art taught recombinant expression in E. coli of a polypeptide with human leukocyte interferon activity, and taught the means for fishing for similar DNA molecules by hybridization, the specifically claimed DNA inserts showed some surprising technical effects as compared to the prior art. The

That the Board is also willing to consider other types of secondary indicia when considering the inventiveness of DNA related inventions was already demonstrated two decades ago in T 500/91*"BIOGEN/Alpha-interferon II"*.[199] In this decision, the Board reiterated that a person skilled in the art would *not* have been able to isolate the specific DNA molecules by application of the common general knowledge. Furthermore, the Board held that because the prior art suggested using a mixed probe, not a unique probe as used by the inventor, the prior art did not promise success to a skilled person faced with the technical problem set out in the patent. Therefore, the claimed invention involved an inventive step.[200] Hence, besides the factual difficulties involved in the modified isolation method, the *skepticism of skilled artisans* before the invention and the *contradicting teaching in the prior art*, or teaching away, apparently served as secondary evidence in the Board's decision.[201]

Furthermore, the Technical Board of Appeals found an inventive step where evidence was presented, showing *others' failure to produce the claimed invention.* In T 343/98 *"Fibroblast growth factor/THE SALK INSTITUTE FOR BIOLOGICAL STUDIES"* the prior art taught bovine basic fibroblast growth factor ("bFGF") polypeptide.[202] The claims were directed to an isolated DNA encoding a mammalian bFGF polypeptide having a particular sequence.[203] However, in addition to the applicant, three companies had attempted to sequence bovine bFGF polypeptide, but all three failed to provide the correct or complete amino acid sequence.[204] Therefore, the Board concluded that sequencing the bovine bFGF polypeptide and isolating the DNA that encodes it must involve an inventive step.[205] This again suggests that secondary considerations may play a role in nonobviousness determinations relating to nucleic acid molecules in Europe.

Similarly, in T 223/96 *"Protein C/ELI LILLY"*[206], the Board found that the lack of availability of a suitable library, and *past failure with available libraries*, was a sufficient indicator of an inventive step. The invention was directed to a full-length DNA encoding human protein C, and the prior art disclosed the isolation and characterization of a partial cDNA encoding human protein C that lacked the 5' end.[207] The Board held that although the skilled person would have readily undertaken to isolate a full-length DNA encoding human protein C using the partial cDNA of the prior art, the isolation of a full-length DNA depended on the availability of a good quality human liver cDNA library.[208] The fact that the prior art had failed to isolate a full length clone from their library confirmed the importance of the

---

claimed DNA inserts were found to serve as a precursor for IFN-alpha2, which was more than 30 times more active than the prior art IFN-alpha1. The structural differences, therefore, conferred a valuable property on the DNA molecules, and the claimed DNA molecules were found to be based on an inventive step).

[199] Case T 500/91, *BIOGEN/Alpha-interferon II* (21 October 1992), (1995) E.P.O.R. at 69, 72 (this was a separate decision relating to the same invention as in case T 301/87, *BIOGEN/Alpha-interferon* (16 February 1989)). *Cf.* Krefft, *supra* note 171, at 154-55 (discussing T 500/91 in the context of particular difficulties in the isolation procedure and comparing it due to the similar underlying facts with the outcome in *In re Deuel*).

[200] *Id.* at para 2.3.4. – 2.4.

[201] I.e. in addition to the high uncertainty at that time and the absence of a sufficient common general knowledge.

[202] Case T 343/98 *"Fibroblast growth factor/THE SALK INSTITUTE FOR BIOLOGICAL STUDIES"* (14 December 2001) at para 8.

[203] *Id.* at para 2.

[204] *Id.* at paras 9 -12.

[205] *Id.* at para 13.

[206] Case T 223/96 *"Protein C/ELI LILLY"* (29 January 1999) at para 26.

[207] *Id.* at paras 1, 22-23.

[208] *Id.* at paras 24-26.

quality of the library.[209] Therefore, the isolation and characterization of the full-length sequence involved an inventive step.[210]

In summary, there is a variety of secondary evidence that the Board might take into consideration when assessing the patentability of biotechnological compounds. Considering the rapid advances in the art of isolation and identification of such substances, as well as the greater quality and availability of sequence libraries, it can be assumed that well substantiated, verifiable reference to such indicia, and in particular unexpected properties, will often be the only possibility to successfully argue for an inventive step. In light of the fast expanding common general knowledge and the increasing predictability of the technology the standard that will be established for such secondary evidence will become ever more crucial to many inventors which will have to constantly monitor the developments.

4. The EPO's position in the Trilateral Projects with special emphasis on gene fragments

Notably, the EPO further clarified its position on the patentability of DNA related inventions in its answers to several hypothetical questions that were raised in the context of the Trilateral Projects with the Japanese Patent Office (JPO) and the United States Patent Office (USPTO).[211] Although a detailed analysis of the outcomes of these projects falls outside the scope of this paper, the EPO's positions in these projects generally confirm the basic principles as they were established in the above described case law. However, since the much debated patentability of DNA fragments was not specifically examined in the previous analysis, the impact that the EPO inventive-step-related answers in the Trilateral Projects have on patent applications concerning partial sequences will now be briefly described below.[212] That the EPO applies a rather rigid inventive-step threshold for such claims is reflected in the reports on the Trilateral Project B3b (ex-24.1) and WM4.

The report on Trilateral Project B3b (ex-24.1) reveals *inter alia* that for ESTs which are not known to code for any particular protein it will be extremely difficult to pass the inventive step hurdle under the "obvious to try with a reasonable expectations of success"-test.[213] This is because the only feature that is usually demonstrated is the mostly routine

---

[209] *Id.* at para 26.

[210] *Id.* at paras 27-28.

[211] The trilateral studies resulted in project reports on various topics, such as 1. Biotechnology Comparative Study on Biotechnology Patent Practices (Trilateral Project 24.1); 2. Patentability of DNA fragments (Trilateral Project B3b (ex-24.1)); 3. Examination Practice Relating to Single Nucleotide Polymorphisms (SNPs) and Haplotypes (Part of Trilateral Project WM4); 4. Comparative study on "protein 3-dimensional (3-D) structure related claims" (Part of Trilateral Project WM4); 5. Mutual Understanding in Search and Examination: Nucleic acid molecule-related inventions whose functions are inferred based on homology search (Trilateral Project B3b); and 6. Biotechnology patent practices: reach through claims (Part of Trilateral Project B3b). All reports are *available at* http://www.trilateral.net/projects/biotechnology.html (last visit: 10 July 2009).

[212] Concerning ESTs, the main concerns of the scientific community can be described as two-fold: *firstly*, that the offices would grant patents for ESTs with no useful function; and *secondly*, that patents would be granted for cDNAs that "comprise" ESTs and thus would be so broad as to include the subsequently discovered corresponding gene. For a more detailed analysis *cf.* Melanie J. Howlett & Andrew F. Christie, *An Analysis of the Approach of the European, Japanese and United States Patent Offices to Patenting Partial DNA Sequences*, INTERNATIONAL REVIEW OF INDUSTRIAL PROPERTY AND COPYRIGHT, Vol. 34, 581-602 (2003); as well as their subsequent publication: *An Analysis of the Approaches of the Trilateral and Australian Patent Offices to Patenting Partial DNA Sequences*, AUSTRALIAN INTELLECTUAL PROPERTY JOURNAL, Vol. 15, No. 3, pp. 156-62 (2004).

[213] In simple terms, ESTs are small pieces of DNA sequence (usually 200 to 500 nucleotides long) that are generated by sequencing either one or both ends of an expressed gene. The idea is to sequence bits of DNA that represent genes expressed in certain cells, tissues or organs from different organisms and to use these easily (re)producible "tags" to fish a gene out of a portion of chromosomal DNA by matching base pairs. Thus ESTs

preparation of the sequence, and a potential routine use as a probe to find the full gene. Yet, such an application generally is not considered to be surprising or unexpected.[214] However, if the EST could be used as a probe to diagnose a particular disease (which will be rarely the case) then the EPO might consider the inventive step requirement to be fulfilled.[215]

Moreover, the comparative studies carried out under Trilateral Project WM4 reveal that the EPO's inventive step requirement will more likely be fulfilled for SNPs[216] that are often associated with disease and/or diagnoses. In other words, identification of a new single nucleotide polymorphism within a known gene may be inventive provided that a novel and non-obvious function can be assigned to it.[217] For example, the function could relate to a relationship between particular polymorphisms and the predisposition towards a certain disease. Thus SNPs might very well be useful for the development of diagnostic methods. Any prior art disclosure of any polymorphisms within the same gene and their association with the same disease, however, will usually render the discovery of further polymorphisms obvious. Likewise, new haplotypes of a known gene may also be inventive provided a new and non-obvious function can be assigned to them.[218]

Notably, at the time of the publication of the Trilateral Project reports the EPO's position on the assessment of the inventive-step requirement for ESTs and SNPs was quite different in comparison to the U.S. non-obviousness approach. Following the teaching of *In re Deuel*, a claim for a DNA sequence is *prima facie* non-obvious if no structural similarity exists between the sequence and what is known in the state of the art.[219] Because a claimed new DNA sequence, or a fragment thereof, is usually different in structure from other DNA or protein sequences known in the state of the art, prima facie non-obviousness was often a mere formality and relatively easy to accomplish for ESTs in particular.[220] However, as it was later confirmed by the CAFC decision in *In re Fisher*[221], it also became clear that the USPTO

---

provide researchers with a quick and inexpensive route for discovering new genes, for obtaining data on gene expression and regulation, and for constructing genome maps.

[214] *See also* Bostyn, *supra* note 66, at 51.

[215] This was the case for the hypothetical claims D and E in Trilateral Project B3b (ex-24.1), which all patent offices considered to entail an inventive step. Yet, the other four claims were rejected by the EPO and the JPO for lack of inventive step. The USPTO, however, acknowledged non-obviousness for all six claims as a mere formality. The stumbling blocks for the claims were, however, the utility and enablement requirements.

[216] In simple terms, SNPs are sites in the genome where there is single-base variation among the population of one particular base in the sequence. They occur approximately once very 1000 bases along the three billion bases of the human gene. SNPs may be responsible for variations between individuals, including variations which predispose an individual to disease or cause it.

[217] *See Trilateral Project WM4*: Report on comparative study on Examination Practice Relating to Single Nucleotide Polymorphisms (SNPs) and Haplotypes *available at* http://www.trilateral.net/projects/biotechnology/Haplotypes.pdf (last visit 30 July 2009).

[218] *See Trilateral Project WM4*, *supra* note 217; *see also*, Howlett & Christie, *supra* note 212, 34 IIC 598 – 602 (2003) & UK Biotech Guidelines, *supra* note 109, at para 36 (Of note: A haplotype is a particular combination of alleles (alternative form of genes) or sequence variations that are closely linked – that is, are likely to be inherited together – on the same chromosome).

[219] *See* Leslie Restaino, Steven Halpern & Eric Tang., *Patenting DNA-Related Inventions in the European Union, United States and Japan: A Trilateral Approach or a Study in Contrast*, 2 UCLA J.L. & TECH. 1, 19-20 (2003).

[220] *See* Krefft, *supra* note 171, at 158-62 (adding, however, at page 158 that an SNP of an already known gene sequence would probably be found to be structurally similar, since it would only be different in non single nucleotide. Thus, even under US law the SNP would have needed to demonstrate surprising properties in order to be held non-obvious). *See also* Bostyn, *supra* note 66, at 51 (adding that "(S)uch an approach does indeed not take into account the processes for preparing and producing these sequences, which, as we have seen above, are automated. The approach of the EPO is therefore in view of the author the better one.").

[221] Noteworthy in this context is the dissenting opinion by J. Rader, in *In re Fisher*, 421 F.3d 1365, 1381-82 (Fed.Circ. 2005), who in rejecting the restrictive interpretation of the utility criteria in 35 USC § 101 stated: "In truth, I have some sympathy with the Patent Office's dilemma. The Office needs some tool to reject inventions

applied the utility and the enablement requirement in a similar restrictive way like the EPO (and the JPO) and would thus have regularly rejected claims on ESTs either because of failure to show a specific substantial and credible utility or because of insufficient description of uses.[222] Given the few hypothetical claims found valid in the comparative study (i.e. claims relating to specific diagnostic applications or surprising properties), it appears therefore that the practice of the patent offices is such that not many ESTs will pass the stringent requirements for patentability. Accordingly, it seems that the fear of numerous EST patents inhibiting later research was by and large also unfounded.[223]

As it will be elaborated in part II, it should further be added that the recent establishment of a higher non-obviousness threshold in *KSR*[224], as well as the subsequent more explicit repudiation of the *In re Deuel* doctrine in *In re Kubin*[225], implies that the USPTO and the U.S. courts now apply a non-obviousness standard that is at least as restrictive as at the EPO. The USPTO and the US courts will regularly reject product-claims on gene fragments without surprising properties, even where the gene fragments are easily isolated and reproduced by predictable, routine methods and with a "reasonable expectation of success". This renders most ESTs obvious even under U.S. law.

5. Interim-conclusions

It can be concluded that the fulfillment of the inventive step criterion for DNA inventions is today a more difficult hurdle to overcome at the EPO than it was some years ago. At least in principle, an inventive step could still be based on the difficulties accompanied with providing, preparing or isolating a specific biological sequence. In view of present day technologies, however, where computer-technology or further automated techniques are routinely applied in the sequencing process and the starting materials are often available, inventors will have an increasingly difficult task in proving that the mere preparation of the DNA sequence or the expression of a protein that is encoded by it, will make the invention non-obvious or inventive. This is similar in the chemical field, where the mere preparation of a chemical compound by routine methods is basically not inventive, except in the event that it would be a new structure. As for DNA sequences, however, a "structural non-obviousness" argument alone is *not* sufficient at the EPO to successfully argue that the provision of, for example, a particular DNA sequence involves an inventive

---

that may advance the "useful arts" but not sufficiently to warrant the valuable exclusive right of a patent. The Patent Office has seized upon this utility requirement to reject these research tools as contributing "insubstantially" to the advance of the useful arts. The utility requirement is ill suited to that task, however, because it lacks any standard for assessing the state of the prior art and the contributions of the claimed advance." He then expressed that a better tool for assessing a sufficient contribution to the useful arts could be found in 35 USC § 103, followed by a strong criticism of *In re Deuel* (incl. reference to academic writing) and the cynical remark that "[u]nfortunately, this court has deprived the Patent Office of the obviousness requirement for genomic inventions."

[222] As a matter of fact the USPTO finally rejected - like the EPO and the JPO - at least four of the six hypothetical claims in Trilateral Project B3b (ex-24.1). Thus despite the differences in detail the USPTO would have arrived at the same result. For a more detailed analysis *see* Howlett & Christie, *supra* note 212.

[223] *See* Howlett & Christie, *supra* note 212, 34 IIC (2003) at 602 (after having found that: "[t]he Trilateral Offices all rejected at least four out of the six claims (the JPO rejected five claims) and thus it seems that the examination practice in relation to ESTs is quite stringent. All offices agree that a DNA sequence that is used as a probe to locate and identify genes of unknown utility will not satisfy the utility requirement. According to the EPO and the JPO, a DNA sequence, obtained by conventional method that shows no unexpected effect and which is assumed to be part of a certain structural gene based on its high homology with a known DNA encoding protein with a known function, will not satisfy the inventive step requirement.").

[224] *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007), 82 U.S.P.Q 2d 1385.

[225] *In re Kubin*, 561 F.3d 1351 (Fed. Cir. 2009).

step if the sequence could be isolated according to routine cloning and screening methods and without inventive effort. Therefore, rapid developments in technology led to the present situation, where the EPO typically requires further proof of an inventive activity before acknowedging an inventive step in accordance with Article 56 EPC.[226] If previously known isolation and annotation methods have not been applied or modified in a non-obvious way, the EPO will likely require demonstration of secondary indicia for inventiveness, including truly unexpected effects and unforeseen functional properties of a claimed sequence. Thus secondary indicia now play a primary role for the inventive step assessment.[227]

The increased difficulty in meeting the inventive step requirement is further emphasized when considering more specifically sequence homologies. It can be assumed that the application of bioinformatics tools in advanced functional homology studies usually does not pose any problems that can only be solved through inventive effort or particular imagination. Consequently, data mining to identify a polynucleotide or a polypeptide homologous to a polynucleotide or polypeptide, having a known function or activity, will typically not involve an inventive step. Moreover, while a specified degree of homology may serve to distinguish the newly identified sequence from one or more known, homologous sequences, it normally cannot serve to establish an inventive step. Therefore, the identification of a human homologue of a previously annotated gene from another species is in the most cases not inventive, and this is usually regardless of the methods used to identify the homologue.[228]

Yet, as indicated above, the identification of unforeseen functions of a novel gene that has *not* been identified by any form of homology searching may still be inventive, though the final outcome will depend upon the techniques used to determine the function and by what is known in the prior art.[229] In particular, claims to uses or applications of genes where the invention lies in the function of the gene may still be allowable, provided that the function has been demonstrated and is inventive. Similarly, with respect to SNPs the EPO will likely acknowledge inventive step if it is shown that it could not be expected that a variation of the sequence can occur at the claimed position, and that this variation can be used, for example, to diagnose a disease state or a predisposition for a disease, or if it can be applied to develop and apply "tailored" individualized medicaments.[230]

---

[226] *Cf.* Andreas Schrell, *Funktionsgebundener Stoffschutz für biotechnologische Erfindungen*, GRUR 782, 786 (2001); Andreas Fuchs, *Patentrecht und Humangenetik*, Mitt., 1, 5 (2000).

[227] As it will be demonstrated in part II, *KSR* and *In re Kubin* have now led to a similar situation in the US.

[228] This has also been confirmed in the recent UK Biotech Guidelines, *supra* note 109, at paras 30-34 (referring to several EPO, as well as similar national decisions and add at para 34: "Whilst each case should be taken on its own merits, it is reasonable to assume that it is generally obvious to (1) identify previously unknown members of a known family by homology, (2) identify a gene in a database on known structural information about the corresponding protein, or (3) to assign a function to a gene by homology comparison with gene(s) of known function.").

[229] Of note: Surprising properties might also still render a gene-homolog inventive. Yet, then it will be very difficult to prove that the property was truly surprising in comparison to the already disclosed homologues gene.

[230] In this context, it should be underlined that the EPC 2000 still explicitly excludes methods for treatment and diagnosis from patentability, now under Article 53 (c) (previously Art. 52 (4) EPC). However, the exclusion applies only to *methods* of medical and veterinary treatment. It does not apply to products, in particular substances or compositions, for use in any of these methods. Thus patents may still be obtained for surgical, therapeutic or diagnostic substances and compositions, and for instruments or apparatuses for use in such methods. However, many details relating to these (and other) exceptions to patentability under Art. 53 EPC 2000 are still heavily debated. This is particularly true for DNA and protein sequences used in such methods. For a wider discussion of recent case law on Article 53 (c), such as the seminal decision of the EPO's Enlarged Board of Appeal in *G 01/04 "Diagnostic Methods"*, OJ EPO 334 (2006); *see also* Sven Bostyn, *No Contact with the Human Body Please! Patentability of Diagnostic Method Inventions after G01/04*, EIPR 238, 244 (2007); David Rogers, *Exclusions from Patentability of Diagnostic Methods Practiced on the Human Body: Article 52 (4) EPC*, JIPL&P 574-6 (2007); Eddy Ventose, *Making Sense of the Enlarged Board of Appeal in*

Last but not least, the brief analysis of the Trilateral Offices' comparative study further demonstrated that the fear of a flood of EST patent claims for probes without useful functions seems to be unjustified in light of the stringent application of the patentability criteria by the EPO. To the extent that the USPTO previously applied a lower inventive threshold on such sequences, it seems as if *KSR* and *In re Kubin* have raised the non-obvious threshold to a level similar to the EPO inventive step threshold. As a result the USPTO and the CAFC now usually hold EST sequences with no surprising properties to be obvious. However, the generally profound practical consequences of the KSR-induced changes in the law of obviousness will be rather limited for ESTs, because even before KSR such sequences would regularly not have met the U.S. utility and written description/enablement criteria as set forth in 35 U.S.C. §§ 101 and 112.

C. Article 56 and the quality of evidence in biotechnology: The "plausibility test"

The definition of an invention as being a contribution to the art, i.e. as solving a technical problem and not merely putting forward one, requires that it is at least made plausible by the disclosure in the application that its teaching solves indeed the problem it purports to solve.[231]

Another important issue that arises in the inventive step assessment relates to the fact that inventors often tend to exaggerate what they have under their control, while not always clearly defining what they have brought into the realm of predictability.[232] Unsurprisingly, such an attitude can frequently be detected in many hastily submitted patent applications in the rapidly developing biotechnological field, which is characterized by fierce international competition and a constant risk that the applicants' claims are anticipated by competitors or academic research publications.

It was for a long time not uncommon that applicants included only little or *no* evidence of the efficiacy upon which the arguments for the presence of *inter alia* an inventive step rely (e.g. biological activity, stability or dissolution rate) in their initial patent-applications relating to, e.g., new biopharmaceutical compounds, new formulations or new polymorphs. The EPO traditionally allowed such evidence to be submitted at a later date provided that any effects demonstrated are at least hinted at in the application as filed.[233] Yet,

---

Cygnus/Diagnostic Method, EIPR 145, 150 (2008); Eddy Ventose, *Patent Protection for Methods of Medical Treatment in the UK*, IPQ 58, 81 (2008); for a specific discussion of the BRCA case, *see* Karolina Anna Herrlinger, *infra* note 336, at 203-19; *see also* A. Sims, *The Case against Patenting Methods of Medical Treatment*, EIPR 43, 51 (2007) and Elizabeth Verkey, *Patenting Medical Methods – Need of the Hour*, JIPL&P 104 - 113 (2007). Note further that the application of the test in relation to methods of surgery has recently been decided by the Enlarged Board of Appeal in case G 01/07 *"Mediphysics/MR methods for imaging vasculature" (15 February 2010)*; *cf.* A. Odell West, *Protecting Surgeons and their Art? Methods for Treatment of the Human Body by Surgery under Article 52 (4) EPC*, EIPR 102, 108 (2008). *See also* the recent decision in G 02/08 *"Dosage regime/ABBOTT RESPIRATORY"* (19 February 2010) (patentability of dosage regime) and in G 02/06 *"Use of embryos/WARF"* (25 November 2008) (patentability of human embryonic stem cells).

[231] Case T 1329/04, *Factor 9/JOHN HOPKINS* (28 June 2005 - Board 3.3.08 - Galligani), at para 12 (Of note: In the following it is referred to the last name of the chairman of the competent Technical Board of Appeal).

[232] *Cf.* Paul Cole, *Patents and scientific integrity*, CIPA 2–10, at p. 3 and fn. 4 (2008), *available at* http://www.cippm.org.uk/images/Paul%20Cole_6_CIPA%20Journal.pdf (last visit 12 May 2009) (citing Richard Freyman, who had stated: "The first principle is that you must not fool yourself – and you are the easiest person to fool. So you have to be very careful about that. After you've not fooled yourself, it's easy not to fool other scientists. You just have to be honest in a conventional way after that." (Freyman was a member of the Rogers Commission investigating the 1986 Challenger disaster, and expressed concern about 'an almost incredible lack of communication' between management and their working engineers which persuaded ordinary citizens to fly in a dangerous machine as if it were an ordinary airliner. He concluded his report with the observation that: "For a successful technology, reality must take precedence over public relations, for Nature cannot be fooled.")).

[233] *Cf.* Former *Guidelines for Examination in the European Patent Office* (December 2007), at C-VI, 5.3.5: "Under certain circumstances... later filed examples or new effects, even if not allowed into the application,

recent case law from the EPO Board of Appeal relating primarily to the inventive step, industrial application and sufficient disclosure requirements indicates that the EPO has now reacted to an increasing number of poorly substantiated patent claims on *inter alia* biopharmaceutical inventions seeking a misleadingly broad scope of protection.[234] These decisions particularly emphasize that the success of a patent application greatly depends on the inventor's ability to demonstrate sufficient understanding of the conditions under which an experiment is carried out so that the claimed results are under the control of the experimenter.[235] The following chapters summarize and analyze the recent case law development in chronological order with a focus on the inventive step assessment.

1. The first developments towards the current "plausibility test"

With respect to the "inventive step" requirement, the "plausibility test" was already reflected in an earlier line of EPO authority, in which claims to broad classes of chemical compounds asserted to have some common technical effect were rejected under article 56 EPC when there was nothing to demonstrate that they would all have that technical effect. The leading case is Case No T 0939/92 "AGREVO",[236] which concerned a product claim for a broad class of chemical compounds that were asserted to share specific properties which made them useful as herbicides. The EPO's Examining Division found, however, that the description did not contain sufficient evidence to substantiate the assertion that all the compounds in the class would share such (herbicidal) properties.[237] The patent applicant, *Agrevo*, argued in response that it was not necessary to show that all the compounds falling within the genus had herbicidal properties. On appeal, this argument was clearly rejected by the EPO Board of Appeal (the Board). The Board underlined that for a long time it has been a generally accepted legal principle that the extent of the patent monopoly must correspond to the technical contribution to the art, and that for patentability a genus of compounds must not

---

may nevertheless be taken into account by the examiner as evidence that the invention can be readily applied, on the basis of the information given in the originally filed application, over the whole field claimed..."; *see also* several cases which principally confirmed this basic rule, such as case T 984/00 "*Ti-plasmid vectors/Max Planck Gesellschaft*" (18.06.2002– Board 3.3.04 – Perryman); case T 397/02 "*Endogenous gene expression/APPLIED RESEARCH*" (10.10.2003 – Board 3.3.08 – Galligani) and case T 1191/03 "*Virusvermehrung/MEYER*" (23.06.2005 – Board 3.3.08 – Galligani). *See also* Allie Elend & Stephen Johnson, *Plausible Pharmaceutical Solutions*, Inside IP - Venner Shipley's Intellectual Property Magazine, 13-15 (Winter 2008/09), *available at* http://www.vennershipley.co.uk/downloads/1_inside_ip_winter08-09s.pdf (last visit: 10 July 2009).

[234] For a more comprehensive overview on the new EPO case law development with regard to the industrial application requirement, *see* Timo Minssen, *„När anses en bioteknologisk uppfinning vara komplett och praktiskt användbar? part II – Om senare utveckling kring kravet på "industrial application" och "utility" för gen- och proteinrelaterade uppfinningar I USA och Europa*, NIR 339 - 387 (2008) (in Swedish). A comparative analysis of the recent "utility" developments in the US is provided in part I, *see supra* note 4.

[235] Cole, *supra* note 232, at 3 (arguing that by being truly concerned with whether and applicant or patentee has a validly patentable invention and reacting to claims of misleadingly broad scope for inventions in empirical research fields, the EPO echoes the above mentioned (fn.232) memorable statement by Richard Feynman.).

[236] *Case* T 0939/92 "*Triazole Herbicides/AGREVO.Herbicides/AGREVO*" (13.12.1991); see also T 0425/91 "*Detergents/Unilever*" (27.02.1996).

[237] Agrevo had reported tests on a large number of compounds, but, as noted by the examining division, in all of them R1 was always either unsubstituted phenyl or 2- pyrimidinyl optionally substituted by methyl groups and R3 was always phenyl substituted by halogen atoms or methyl groups. Thus, despite the fact that the specification disclosed a number of compounds and test data for those compounds, the Board held that these test results did not support the alleged herbicidal activity across the whole breadth of the claim. For example, it pointed out that because claim covered compounds in which the phenyl ring in position R3 could have any substituent whatsoever, the range of possible substituents included substituents detrimental to herbicidal activity, especially having regard to the common general knowledge that the influence of structural modifications on the desired herbicidal activity is unpredictable. *See id.* at paras 1-2; *see also* Cole, *supra* note 232, at 4 (further illustrating this point).

represent a mere arbitrary selection but must be justified by an unknown technical effect that is caused by those structural features, which distinguish the claimed compounds from the numerous other compounds.[238] With regard to the facts, the Board decided that, while a skilled artisan would have been able to make all the compounds claimed and that the claims in question therefore could be considered to be sufficiently described,[239] they would nevertheless fail for lack of an inventive step because simply producing the compounds involved no inventiveness. The invention, if any, would be based on the discovery of their advantageous herbicidal properties and their potential uses as herbicides.[240] The Board particularly emphasized that it was further necessary not only that some of the claimed compounds had herbicidal activity, but that they all did. The Board held that:

"It follows directly from these considerations that a technical effect which justifies the selection of the claimed compounds must be one which can be fairly assumed to be produced by substantially *all the selected compounds."*[241]

At paragraph 2.6.2 the Board then stressed, as undisputed common general knowledge, that even small structural modifications may cause major differences in biological activity and that herbicidal activity was thus difficult to predict for all the claimed compounds. Yet, the Board also acknowledged that it is well accepted that the properties of chemical compounds do indeed largely depend on their chemical structure, and that a skilled person would therefore normally expect that the properties of two compounds would become the more similar the more similar their chemical structures became.[242] Consequently, the Board affirmed that while a patentee does not necessarily need to have in fact experimentally tested every compound to see whether it has the claimed effect, any predictions could only be accepted as reasonable when they are based on valid (e.g. structural) evidence. The Board held in particular:

"In view of all the above considerations, the Board finds that reasonable predictions of relations between chemical structure and biological activity are in principle possible, but that there is a limit beyond which no such prediction can be validly made."[243]

---

[238] *Id.* at para 2.4.2 (referring to case T 409/91, OJ EPO , No. 3.3. and 3.4 of the reasons, and case T 435/91, OJ EPO 1995, 188, reasons No. 2.2.1 and 2.2.2). With regard to the relationship between the sufficient disclosure requirement in Article 83/84 EPC and the inventive step requirement in Article 56 EPC the Board added: "Now, whereas in both the above decisions this general legal principle was applied in relation to the extent of the patent protection that was justified by reference to the requirements of Articles 83 and 84 EPC, the same legal principle also governs the decision that is required to be made under Article 56 EPC, for everything falling within a valid claim has to be inventive. If this is not the case, the claim must be amended so as to exclude obvious subject-matter in order to justify the monopoly." *Cf.* para 2.6 of the judgment.

[239] *Id.* at para 2.2.2. *See also* headnote I of the judgment ("If a claim concerns a group of chemical compounds per se, an objection of lack of support by the description pursuant to Article 84 EPC cannot properly be raised for the sole reason that the description does not contain sufficient information in order to make it credible that an alleged technical effect (which is not, however, a part of the definition of the claimed compounds) is obtained by all the compounds claimed.").

[240] *Id.* at paras 2.4 to 2.6. *See also* headnote II of the judgment ("II. The question as to whether or not such a technical effect is achieved by all the chemical compounds covered by such a claim may properly arise under Article 56 EPC, if this technical effect turns out to be the sole reason for the alleged inventiveness of these compounds.").

[241] *Id.* at para 2.5.4 (referring to case T 131/87 of 7 September 1989 at para 8; case T 742/89 of 2 November 1992 at para 7.4; case T 626/90 of 2 December 1993 at para 4.3.2; and case T 741/91 of 22 September 1992 at paras 4.2 and 4.3). *See also id.* at para 2.6.2 ("In the present case, the Appellant's submission that the test results contained in the description show that some of the claimed compounds are indeed herbicidally active, cannot be regarded as sufficient evidence to lead to the inference that substantially all the claimed compounds possess this activity. The reason for this is that there is no proven common general knowledge to show that the type of substituent that may be present in the claimed compounds would be irrelevant to the existence of the alleged herbicidal activity (...).").

[242] *Id.* at para 2.6.2 (referring to decision case T 181/82, OJ EPO 1984, 401, No. 5 of the reasons).

[243] *Id.*

Taking into account common general knowledge, the Board then examined the available facts and evidence submitted by the applicant and found that the evidence did not permit the prediction that substantially all claimed compounds were likely to be herbicidally active. The Board concluded that because only those of the claimed chemical compounds could possibly involve an inventive step, which could be accepted as solutions to the technical problem of providing further herbicidally active compounds, the subject-matter of the main request extends to compounds that are not inventive and therefore does not meet the requirement of article 56 EPC.[244]

The "AGREVO" principles relating to the level of proof necessary to demonstrate that a claimed invention involved an inventive step under Article 56 EPC have now been further manifested and developed in a recent line of EPO case law involving mostly biotechnological and, in particular, DNA-related inventions. The most significant case for the inventive step assessment was *T 1329/04 "Factor 9/JOHN HOPKINS"*, [245] which was followed by many critical comments from worried patent practitioners. More specifically, this case addressed the crucial question of whether the use of the claimed product that may constitute the inventive step must be stated in the specification or could be proved by evidence at a later date. The claim at issue was directed to a new DNA sequence encoding a (also claimed) polypeptide with the SEQ ID No.3 "having GDF-9 activity", the patentability of which was argued on the basis that it was a new member of the useful TGF-β superfamily.[246] As in AGREVO, there was indeed nothing inventive in merely producing the DNA sequence. The inventive step, if any, would have to be founded on a disclosure that the claimed DNA sequence could in fact be used to produce a useful protein. Yet, the specification disclosed no more than vague speculations about how the GDF-9 activity might be useful for *inter alia* fertility treatment. In particular, GDF-9 did not exhibit all of the structural features shared by the proteins of the TGF-β superfamily and it could not be attributed to any of the subgroups in the family on the basis of sequence homology.[247] Moreover, no data were available to sufficiently support the assertion that GDF-9 would play any one of the roles known to be fulfilled by TGF-β family members. Under these circumstances the examining division rejected the application on the ground that such speculation did not go beyond what was obvious. It also refused to take into account subsequently submitted evidence based on *inter alia* "wet-biology" experiments that demonstrated that the claimed "GDF-9"-polypetide actually had such properties.[248]

On appeal the Board initially indicated that even in the absence of any functional evidence it would perhaps have accepted that the protein belonged to the TGF-β superfamily, *if* the compound had exhibited the relevant structural features. One reason for this attitude was that in the prior art it had already been accepted on this basis that another compound,

---

[244] *Id.* at para 2.7.

[245] Case T 1329/04 *"Factor 9/JOHN HOPKINS"* (28 June 2005 – Board 3.3.08*). See also* Hans-Rainer Jaenichen, *Reduction to Practice: All Inventions Are Created Equal: Refinement of T 1329/04 in Favor of the Completeness of DNA Inventions Without Wet Biology Experiments*, 26 Biotechnology Law Report 5, 6 (2007) (referring further to an slightly earlier decision of the same Board which demonstrated that the "plausibility-test" can also support patent applications with regard to the novelty assessment. He pointed out that in T179/01 "Herbicide resistant plants/MONSANTO" the Board took the position that a prior art disclosure of an open reading frame and its hypothetical function, which was not supported by experimental evidence, was not prior art that precluded the novelty of a later-filed claim covering the DNA sequence of the same disclosed open reading frame. In other words, a purely hypothetical prior art disclosure did not amount to a complete technical teaching and thus was irrelevant as invalidating prior art.").

[246] More specifically, the applicant claimed this polypeptide "GDF-9" to be a new member of the TGF-β superfamily, since it had a sequence homology of 34% with other TGF-β superfamily members. Yet, it had only six of the seven particularly spaced cysteine residues that were held to be typical for TGF- β members.

[247] *Id.* at I and at paras 7 and 8 of the reasons for the decision.

[248] *Id.* at I.

GDF-1, was a member of the TGF-β superfamily.[249] Conversely, as the pending application did not provide any satisfactory evidence to this effect,[250] the Board concluded that GDF-9 had not been demonstrated to be a *bona fide* solution to the problem to be solved. More precisely, the Board pointed out in paragraph 10 that in the specification various effects were "tentatively and presumptively" attributed to GDF-9. The Board found further that:

> [T]he issue here is...how much weight can be given to speculations in the application in the framework of assessing inventive step, which assessment requires that facts be established before starting the relevant reasoning. In the board's judgment, enumerating any and all putative functions of a given compound is not the same as providing technical evidence as regard a specific one...[T]here is not enough evidence in the application to make at least plausible that a solution was found to the problem which was purportedly solved.

The Board then underlined again in paragraph 12 that the definition of an invention as being a contribution to the art, i.e. as solving a technical problem and not merely putting forward one, requires that it is at least made "plausible" by the disclosure in the application that its teaching solves indeed the problem it purports to solve.

Considering further whether the lack of plausibility could be remedied by evidence coming into existence after the application, the Board held that even if supplementary post-published evidence may in the proper circumstances also be taken into consideration, it may *not*, for the reasons mentioned above, *serve as the sole basis* for demonstrating that the application indeed solves the problem it claims to solve.[251] Applying these principles to the facts of the case, the Board therefore decided that the post-published evidence submitted by the applicant could not be regarded as supportive of evidence which would have been previously submitted in the application as filed because the original patent application did not contain *any* evidence to render the claimed invention as pausible. As the post-published evidence was considered to be the first disclosure going beyond speculation it was not taken into consideration. Consequently, the Board upheld the decision of the examining division and the application was rejected for failing to fulfill the requirements of Article 56 EPC.

The significance of the "plausibility test" for the inventive step assessment, and in particular for the success of arguments relating to unexpected effects, was further confirmed by the same Board in T 1306/04 *"Cell death peptide/ONO"*[252]. This case concerned an

---

[249] *Id.* at para 3.

[250] In particular, the Board found that the absent cysteine residue of the conserved seven cysteine domain would raise justified doubts in the mind of the skilled artisan about whether GDF-9 indeed was a new member of the TGF- β superfamily. There was no sufficient experimental support in the application as filed, and there were no expert declarations to disperse these doubts, for example, by confirming that the absent structural feature would not have justified serious doubts about the function of the protein in the mind of the skilled artisan.

[251] *Id.* at para 12 ("The appellant filed post-published evidence... establishing that GDF-9 was indeed a growth differentiation factor. This cannot be regarded as supportive of an evidence which would have been given in the application as filed since there was not any. The said post-published documents are indeed the first disclosures going beyond speculation. For this reason, the post-published evidence may not be considered at all. Indeed, to do otherwise would imply that the recognition of a claimed subject-matter as a solution to a particular problem could vary as time went by. Here, for example, had the issue been examined before the publication date of the earliest relevant post-published document, GDF-9 would not have been seen as a plausible solution to the problem...and inventive step would have had to be denied whereas, when examined thereafter, GDF-9 would have to be acknowledged as one such member. This approach would be in contradiction with the principle that inventive step, as all other criteria for patentability, must be ascertained as from the effective date of the patent. The definition of an invention as being a contribution to the art, i.e. as solving a technical problem and not merely putting forward one, requires that it is at least made plausible by the disclosure in the application that its teaching solves indeed the problem it purports to solve. Therefore, even if supplementary post-published evidence may in the proper circumstances also be taken into consideration, it may not serve as the sole basis to establish that the application solves indeed the problem it purports to solve.").

[252] Case T 1306/04 *"Cell death peptide/ONO"* (8 December 2005 – Board 3.3.08).

applicant's appeal against the Examining Division's decision to refuse its patent application regarding a novel peptide related to human programmed cell death and the DNA encoding it. The technical contribution to the state of the art was a cDNA isolated from a human cell line which encoded a protein called "human PD-1." Claim 1 read:

"1. A polypeptide in substantially purified form having the amino acid sequence shown in SEQ. ID. No. 1 or amino acid sequence having at least 90% homology with the amino acid sequence shown in SEQ. ID. No. 1."

The closest state of the art described the activation of a cell-death associated gene, termed PD-1, in two murine lymphoid cell lines and the isolation of a cDNA clone from a related cDNA library. The document also disclosed the structure of this murine cDNA and the predicted amino acid sequence of the corresponding protein, i.e. the murine PD-1 protein.[253] Thus, the Board regarded the technical problem to be solved as the provision of a protein homolog of the murine PD-1 protein from an organism other than a mouse.[254]

Yet, other documents in the prior art already announced that a human ortholog existed that had high homology with the murine PD-1 sequence.[255] In light of this prior art, the Board opined that a person skilled in the art would have been prompted to investigate human cell lines for the presence of a human homologue. Moreover, the Board believed that in doing so, the person skilled in the art would have had a "reasonable expectation of success." In that regard, the Board specifically rejected the arguments of the appellant who, relying on weak and incoherent evidence, had claimed that the skilled person would not have considered it as credible that a human homologue of the murine PD-1 protein would exist.[256] In addition, the applicant was unable to substantiate any special difficulties or any further unusual problem encountered in cloning the claimed human ortholog.[257]

The last argument for inventive step presented by the applicant was that the beneficial use of the human PD-1 cDNA in the diagnosis of a systemic disease (lupus erythomatosus) was an *unexpected advantage*. The application, however, made no mention of this specific use for which probable evidence could only be produced and substantiated some eight years after the priority date. In light of these circumstances, the Board refused to accept this argument and turned to its plausibility test:

"Here, the appellants are reminded of the case law of the Boards of Appeal (see, in particular, T 1329/04 of 28 June 2005, point 12 of the reasons) relating to the unsuitability, when assessing inventive step, of taking post-published documents into consideration if the effect taught in these documents is not made at least plausible in the patent application per se. In accordance with this case law, the Board does not consider the argument to be convincing."[258]

Thus, the application was finally refused for not complying with the inventive step requirement in Article 56 EPC.

2. Early concerns

The vehement reactions from patent practitioners following the decisions in T 1329/04 and T 1306/04 must be regarded in the context of a more general development in EPO case law that demonstrated the further impact of the new "plausibility test" on the

[253] *Id.* at para 3.
[254] *Id.* at para 4.
[255] *Id.* at para 6.
[256] *Id.* at paras 7-8 (holding: "The submission made at the oral proceedings that it was known from 2002 onwards that the proportion of mouse genes with a single identifiable orthologue in the human genome seemed to be approximately 80% and that the proportion of mouse genes without any homologue detectable in the human genome (and vice versa) seemed to be less than 1%, if to be taken into account at all, does not speak in favour of a lack of reasonable expectation of success when cloning the human PD-1 cDNA.").
[257] *Id.* at paras 9-12.
[258] *Id.* at para 13.

industrial application (Art. 57 EPC) and sufficient disclosure requirement (Art. 83 EPC).[259] In particular, the combined reading of T 1329/04 and the industrial applicability -related decision in T 870/04 *"BDP1-Phosphatase/MAX-PLANCK"*[260] gave the clear impression that the EPO had adopted a much stricter attitude and would now require more persuasive evidence, not only to demonstrate a plausible solution to a problem in the context of the inventive step assessment, but also to prove that the claimed invention actually can be applied in industry.

In T 870/04 the Board decided that the industrial applicability requirement was not fulfilled by a patent application claiming a newly identified polypeptide and its asserted uses in, *inter alia*, cancer treatment. Although the Board was aware of earlier jurisprudence which had been rather generous in similar situations,[261] and acknowledged that the claimed polypeptide could, at the relevant date, very well be regarded as a significant scientific achievement and an interesting object for further research, it highlighted that the concerned field of potential application was very much unexplored. In addition, the Board directed special concern to the facts that none of the submitted evidence could, at the date of application, convincingly demonstrate the claimed uses. In reaching its decision, the Board then used language similar to that in the U.S. Supreme Court decision, *Brenner v. Manson*, which was subsequently invigorated by the CAFC in *In re Fisher*,[262] and held that:

> ... although the present application described a product (a polypeptide), means and methods for making it, and its prospective use thereof for basic science activities, it identifies no practical way of exploiting it in at least one field of industrial activity. In this respect, it is considered that a vague and speculative indication of possible objectives that might or might not be achievable by carrying out further research with the tool as described is not sufficient for fulfillment of the requirement of industrial applicability. The purpose of granting a patent is not to reserve an unexplored field of research for an applicant.[263]

---

[259] *Cf.* the more restrictive decisions with a focus on the industrial application requirement under Art. 57 EPC in case T 870/04 "*BDP1-Phosphatase/MAX-PLANCK*" (11 May 2005 - Board 3.3.08 - Galligani). A detailed analysis of these cases is provided by Minssen, *supra* note 234, at part II. Compare further the rather strict application of the "plausibility test" in the context of the Art. 83 EPC assessment (sufficient disclosure) in the following decisions: case T 792/00 "*Varied binding proteins/Dyax*" (2 February 2002- Board 3.3.08 – Galligani) (holding at para 3-5 that if for an invention which goes against prevailing technical opinion the patentee has failed to give even a single reproducible example, sufficiency of disclosure cannot be acknowledged. Yet, as it is then shown a para 9-11 that hypothetical examples may still be used. However, if the hypothetical experimental protocol is the only example to be relied on for showing sufficiency, then the burden of proof lies on the patentee to show that in practice this protocol works as stated. Evidence that a variation of the protocol works is unlikely to be enough); case T 497/02 "*Insulinotropic hormone/ General Hospital*" (27 May 2004 – Board 3.3.04 - Kinkeldey) (holding that if the technical content of a patent application concerning a protein-related pharmaceutical invention is judges fundamentally insufficient under Art. 83 EPC as of the filing date, then it is not possible to remedy the situation by submitting late-filed experimental evidence); and case T 0609/02 "*AP-1 complex/SALK INSTITUTE*" (27 October 2004 – Board 3.3.08 - Galligani) (holding that human clinical trials or animal data would not always necessarily be required to establish a sufficient disclosure of a therapeutic effect and that coherent *in vitro* evidence might still be sufficient. Yet, if the description of a patent specification provides no more than a vague indication of a possible medical use for a chemical compound yet to be identified, more detailed evidence cannot later be used to remedy the fundamental insufficiency of disclosure.).

[260] Case T 870/04 "*BDP1-Phosphatase/MAX-PLANCK*" (11 May 2005 – Board 3.3.08 - Galligani).

[261] *Id.* at para 6 ("While the jurisprudence has tended to be generous to applicants, there must be a borderline between what can be accepted and what can only be categorised as an interesting research result, which per se does not yet allow a practical industrial application to be identified.").

[262] *Brenner v. Manson*, 383 U.S. 519, 535–536 (1966) (stating "(a) patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion"); *cf. In re Fisher*, 421 F.3d 1365, 1376 (Fed.Cir. 2005).

[263] Case T 870/04 "*BDP1-Phosphatase/MAX-PLANCK*" at para 21 (after having previously established at para 4 that, "(t)he requirement of Article 57 EPC... emphasizes that a 'practical' application of the invention has to be

Considering these developments, unsurprisingly, many patent attorneys expressed strong concern and vehemently criticized the potential consequences of the new case law. Aware of the fierce international competition they had traditionally advised their clients to apply as soon as possible for patent protection. In doing so, they had previously relied on the EPO's Examination Guidelines and earlier case law, which had established the general principle that an invention need only be "performable" at the relevant date of the patent application, and that additional experimental "in silicio" or "wet biology" evidence would still be accepted even if submitted at a later date.[264]

According to some patent attorneys, the aforementioned decisions suggested that comprehensive experimental evidence would be required from now on for DNA inventions to demonstrate that they are sufficiently complete for a determination of the primary patentability requirements of industrial applicability, enablement, novelty and inventive step. It was asserted that the Board had coined the "plausibility test" as and apparently overly strict test to be conducted by a person skilled in the art as a means to determine an invention's completeness at the filing date. Because the EPO would only consider post-filing data in support of the correctness (and thus the completeness) of what had been disclosed at the filing date, if the "plausibility test" was fulfilled, some practitioners feared that the new developments had the potential to significantly restrict the issuance, not only of DNA inventions, but also of many other kinds of inventions in other technical areas. One concern was that an EPO requirement for experimental evidence in the original application to demonstrate reduction to practice at the filing date could change the established "performable is sufficient" principle to a "performed is required" principle. This could potentially weaken European patent applicants in their competition with U.S. applicants, where the "performable is sufficient principle" still seems to represent the general rule,[265] despite some recent decisions reflecting a stricter approach with regard to the quality of the necessary evidence.[266]

---

disclosed. Merely because a substance... could be produced in some ways does not necessarily mean that this requirement is fulfilled, unless there is also some profitable use for which the substance can be employed.").

[264] *Cf.* e.g. the former *Guidelines for Examination in the European Patent Office* (December 2007), at C-VI, 5.3.5: "Under certain circumstances...later filed examples or new effects, even if not allowed into the application, may nevertheless be taken into account by the examiner as evidence that the invention can be readily applied, on the basis of the information given in the originally filed application, over the whole field claimed..."; *cf.* several cases that principally confirmed this basic rule, like e.g. case T 984/00 *"Ti-plasmid vectors/Max Planck Gesellschaft"* (18.06.2002 - Board 3.3.04 - Perryman) and case T 397/02 *"Endogenous gene expression/APPLIED RESEARCH"* (10.10.2003 - Board 3.3.08 - Galligani); case *T 1191/03 "Virusvermehrung/MEYER"* (23.06.2005 - Board 3.3.08, Galligani). A more comprehensive overview on similar national, EPO and also US decision is provided by F. Stolzenburg/Barbara Ruskin/Hans-Rainer Jaenichen, *"Of incomplete complete inventions,"* epi Information, 15– 27 (Nr. 1/2006); Compare also Rainer Moufang, in: Schulte, *"Patentgesetz mit EPÜ"* (Heymanns, 8 th edition, 2008), annotation 53-59 to § 1 of the German Patent Act (GPA) and Article 52 EPC, as well as annotation 37 to § 4 of the GPA and Article 56 EPC.

[265] *See* Stolzenburg/Ruskin/Jaenichen, *supra* note 264, at 26 (arguing: "- The test deviates from established jurisprudence in the EPO and ... Germany;... – The test cannot be justified by reference to the EU Biotech Directive because... [t]he disclosure of a function is sufficient. – Because the subjective is to be carried out by the average person skilled in the art,..., it leads to undesirable results; ... – The test is unnecessary to avoid any relevant variation in the assessment of patentability with time...; – The test is to scientific in terms of putting to much emphasis on the presence scientific data rather than applying the traditional legal principle of conception of an enabling invention... The test would put inventors at further disadvantages in the first-to-file patent system over the current (US) first-to-invent patent system. Effective filings would be further delayed by having to do (additional) experiments"); *see also* F. Stolzenburg/Barbara Ruskin/Hans-Rainer Jaenichen, *Von unfertigen fertigen Erfindungen*, GRUR Int. Heft 10, 798–809 (2006), Nina L. White, *Time waits for no man: deciding when to file a patent application in Europe*, 25 NATURE BIOTECHNOLOGY Nr. 6, 639-41 (2007).

[266] See eg. *Rasmussen v. SmithKline Beecham Corp.*, 413 F.3d. 1318, 1323 (Fed. Cr. 2005) (where it was held in an interference proceeding that the evidence must be so convincing that a PHOSITA would accept "without question" the statements concerning the effects of the claimed pharmaceuticals.).

It was further admonished that the inherently subjective character of the "plausibility" test implied a danger for legal certainty, since the new case law did not clearly indicate which type of evidence would be sufficient to make assertions included in a patent application "plausible" to a person skilled in the art. In particular, the case law did not clarify whether a patent application would from now on be required to include data from "wet biology experiments" or whether coherent hypothetical evidence and "in silicio" experiments would still be sufficient to demonstrate, e.g. in the course of the inventive step assessment, that the solution to a problem was plausible.[267] In summary, two central questions remained to be solved: (1) How much data of what quality was needed to obtain a patent?, and (2) When would this data have to be submitted?

3. Recent refinement of the case law

Fortunately, several judgments from the EPO's Board of Appeals that were decided during the last three years have now refined the new principles for the assessment of Art. 56, 57 and 83 EPC.[268] Although these judgments basically confirmed the more restrictive EPO approach and regularly refer to decisions like T 870/04 and T 1329/04, they have also demonstrated that the Board is well prepared to conduct a detailed case-by-case assessment and is willing to consider the specific objective circumstances that surround the invention at issue. In particular, it became clear that the Board will still carefully consider the prior art and the common general knowledge at the relevant date and will not always require *wet-biology experiments* at the date of the first application. In some cases, coherent hypothetical evidence

---

[267] *See* Stolzenburg/Ruskin/Jaenichen, *supra* note 264, at 26-27.

[268] The following analysis will focus on cases that were of particular importance for Art. 56. Yet, *see also* the Art. 57 EPC related findings in case T 604/04 "*PF4A receptors/GENENTECH*" (16 March 2006 – Board 3.3.08 - Galligani); case T 898/05 "*Hematopeitic receptor/ZYMOGENETICS*" (7 July 2006 – Board 3.3.08 - Galligani) (the Board pointed out that DNA related patent applications cannot be refused solely because they base their technical conclusions on DNA sequence (gene) homologies to better known genes or on predicted functions based on "high quality" computer assisted analysis. A guess that was sufficiently supported and plausible was found to be sufficient); case T 641/05 "*GPCR-like receptor/PHARMACIA*" (9 November 2006 – Board 3.3.08 - Galligani) (denying industrial applicability and finding at para 14: "Although, under certain conditions, the board is well prepared - following the case-by-case approach adopted in decision T 898/05 (supra) - to acknowledge a possible function based on computer-assisted methods ...., in the present case the probative value of these (sequence homology) methods is completely lacking"); case T 1452/06, 1452/06 *"Serine protease/BAYER"* (10 May 2007 – Board 3.3.08 – Rennie-Smith); and case *T 1165/06 "IL-17 related polypeptide/SCHERING"* (19 July 2007 – Board 3.3.08 - Galligani). Compare also the UK High Court decision in *Eli Lilly & Company v. Human Genome Sciences, Inc.*, EWHC 1903 (High Court, 31 July 2008) (Kitchin J.) which confirmed the Art. 57 EPC principles established by EPO case law in the national context. The decision had been appealed and has very recently been affirmed by the UK Court of Appeal in *Eli Lilly and Co. v. Human Genome Sciences Inc.*, (2010) EWCA Civ 33 (Court of Appeal, 9 February 2010)(Jacob, J.). For a detailed analysis of Judge Kitchin's preceding decison with an emphasis on Art. 57 EPC *see* Minssen, *supra* note 234, at part II. Regarding the sufficient disclosure requirement under Art. 83 EPC *cf.* the following cases: Case T 1262/04 "*Light detection in mammals/LELAND STANFORD*" (7.3.2007 - Board 3.3.04-Kinkeldey) (noting that the description in the application did not disclose, by way of experimental report, methods which fell within the ambit of the claims, the Board nevertheless considered that the general part of the description of the application disclosed ample technical detail and measures which enable in a credible manner to work the invention as claimed. Considering these circumstances and referring to two earlier decisons (T 994/95 and T 157/03), the Board also considered post-published documents that provided evidence that the invention was indeed reproducible without undue burden at the relevant date. Thus it was decided that the Art. 83 criteria were met). *See also* the earlier decision in case T 0127/02 "*Herpesvirus Mutants/HARVARD*" (16.09.2003 – Board 3.3.08 - Galligani) (here the Board paid special attention to the well developed prior art and saw no particular technical problem or special difficulty for the skilled person to put into practice the teachings disclosed in the application, ie preparing a medicament for the treatment of herpetic stromal keratitis. The fact that no specific experimental data was submitted at the relevant date did not render the teaching insufficient).

of a higher quality than in 1329/04 was accepted, sometimes including data that was provided by *in silicio* or in *vitro trials*. Under such circumstances, the Board was also prepared to consider post-published evidence in support of the qualified and plausible assertion. On the other hand, if the Board considered the quality of the evidence that was submitted at the relevant date of the application to be of a lower quality and not "plausible", or if the evidence on which basis the inventive step assessment could have been conducted was completely missing, then post-published evidence will not likely be accepted to support the initial assertions even if the assertions were later proven to be correct.

To demonstrate the more recent developments in the context of the inventive step requirement, it is particularly worth to mention two cases from the same Board that had earlier decided T-1329/04 and T 1306/04, i.e. Board 3.3.08, as well as two further interesting cases subsequently decided by the other "biotech" –board, i.e. Board 3.3.04[269]:

In *T 1336/04 "Cellulase/NOVOZYME"*[270] Board 3.3.08 (this time chaired by Davison-Brunel) was confronted with a technical situation that was rather different from 1329/04, namely one where the quality of evidence provided in the respective patent was such that the claimed invention was considered to be a *bona fide* solution to the problem to be solved. More specifically, the decision dealt with a patent holder's appeal from the Opposition Division's decision to revoke a patent, which related to the cloning of fungal genes encoding cellulose- or hemicellulose-degrading enzymes. Claim 1 of the main request related to the encoded enzymes:

> 1. A cellulose- or hemicellulose-degrading enzyme which is derivable from a fungus other than Trichoderma or Phanerochaete, and which comprises a carbohydrate binding domain homologous to a terminal A region of Trichoderma reesei cellulases, wherein the carbohydrate binding domain comprises the following amino acid sequence [ten partial amino acid sequences follow] or a subsequence thereof capable of effecting binding of the enzyme to an insoluble cellulosic or hemicellulosic substrate.

The prior art included an article on cellulose families and their genes from bacteria and fungi. Disclosing some fungi cellulases and their genes, the paper suggested a way to enhance the current industrial processes by optimizing the available enzymes, either by finding new enzymes and genes from nature or even by protein engineering.[271] Starting from this closest prior art reference, the Board identified the technical problem that was

---

[269] Among the more interesting recent EPO cases which equally demonstrate the refinement of the Art. 56 related "plausibility" assessment of the Board of Appeals, but which canot be analyzed in detail due to page limitations are: case T 293/04 *"Lyme vaccine/BAXTER"* (05.04.2006 – Board 3.3.08 - Mennessier) (confirming that coherent hypothetical evidence of a "high quality" which is supported by prior art experience can still be accepted as a plausible *bona fide* solution in the Art. 56 EPC assessment); case T 710/05 *"NMDA oxidizing agents/CHILDREN'S MC"* (22.02.2007 – Board 3.3.08 - Galligani) (concerning a situation where no evidence of any kind was given to support the assertion of specific therapeutic effects, while the prior art taught that mechanisms different from those in the claims were involved in the process at issue which left completely open the possibility that the claimed therapeutic effect (i.e. the protection of neural cells from toxicity) was not existent. Thus, the Board held at paragraph 21 that the application could not make the assertion plausible and concluded at para 22-23 that the situation was analogous to the situation in 1329/04 and that thus the provisions of Art. 56 were not fulfilled); *see also* case T 903/05 *"Telomerase peptides/GEMVAX"* (30.08.2007 – Board 3.3.04 - Wieser) (one of the appellants interestingly submitted in the context of the priority assessment under Art. 87 to 89 EPC that in view of T 1329/04, it would be necessary that the priority document contained experimental data which made plausible that the claimed invention worked. Yet, the Board held at paras 12-14 that T 1329/04 is concerned with the question of inventive step and is therefore not relevant for the present issue of entitlement to priority. Thus, the Board decided that the priority date of the patent in suit was validly claimed).

[270] Case T 1336/04 *"Cellulase/NOVOZYME"* (9 March 2006 – Board 3.3.08).

[271] *Id.* at para. 8.

purportedly solved by the patent in suit to relate to the provision of alternative fungal cellulases and their genes. In that regard the Board stated:

> The subject-matter of claim 1 indeed relates to novel cellulose- or hemicellulose-degrading enzymes as characterized by the homology of their CBDs to that of known cellulases. The endoglucanase activity of one of these enzymes is also shown in document (16). On this basis, the board accepts that the above mentioned problem was satisfactorily solved. In this context, it is worth noticing that the present situation is different from that underlying the decision T 1329/04 (supra) as to the quality of evidence provided in the patent in suit relating to the claimed invention being a *bona fide* solution to the problem to be solved. [272]

Under these particular circumstances, the Board not only accepted the solution of the problem which was presented in the original patent application as plausible but was, at least to some extent, also willing to take into consideration the disclosure in a post-published document (document 16) as a valid supplement to the plausible technical contribution disclosed in the patent (-application).[273]

However, it was then also clearly demonstrated by T 1336/04 that the mere fact that the Board accepts a *bona fide* solution to an identified problem as plausible *not* necessarily implies that this solution would also be held to be *inventive*. In particular, the Board found that at the priority date of the patent (9 May 1990), it was within the realm of common general knowledge,that powerful tools of modern molecular biology could be used to explore in detail the complexity of ligocellulose degradation and that identifying further cellulase genes was therefore "obvious to try".[274] Addressing the appellant's counter argument, that the particular choice of the probe to be used for screening the recombinant clones would not have been obvious to the skilled person, the Board highlighted that the prior art further disclosed that cellulases display some common features in their architecture, such as the presence of particular domains, despite the great variety in their structure and the dissimilarities in their primary structures.[275] Under these circumstances, the Board considered that it was obvious to construct and select the probe used by the appellant in order to identify, isolate and clone as many cellulases as possible, independently of their class and type, just as it was obvious to use a probe comprising the full-length sequence of a particular class of cellulases to screen fungi libraries for the presence of corresponding genes encoding this very particular class of cellulases. Thus the Board saw no inventive contribution in the *selection of the particular screening probe*.[276]

In view of the detailed disclosure of the prior art, the Board also held that selecting the rather well known cellulolytic fungi as the starting material for cloning would have been obvious to a skilled artisan. The Board further pointed out that the skilled person would have successfully identified and isolated the claimed encoding genes, and consequently the claimed enzymes, in a direct and straightforward manner and that no technical difficulties would have been expected by the skilled person. Thus the Board found that neither the *cloning strategy* disclosed in the patent involved an inventive step.[277]

---

[272] *Id.* at para. 9.

[273] The Board thus accepted some of the arguments of the appellant, who had *inter alia* contended with regard to the post published document 16: "Although filed in 2004, this evidence could be taken into account in the assessment of inventive step because it supplemented the technical contribution disclosed in the patent. The present situation was thus different from the one underlying decision T 1329/04 of 28 June 2005, in which inventive step was denied because it was solely on the basis of post-published evidence that the then claimed subject-matter could be identified as a *bona fide* solution to the problem to be solved (*cf. id.* point XIII)."

[274] *Id.* at para 10.

[275] *Id.* at para 11 (emphasizing *inter alia* that the terminal domain was known to be conserved because there was a close evolutionary relationship caused, in some cases, by gene duplication).

[276] *Id.* at paras 12-13.

[277] *Id.* at paras 15-16.

Next, the appellant wanted to rely on *unexpected properties* of the claimed enzymes. In doing so, the appellant once again referred to the post-published document (16), arguing that the document showed that the EGV enzyme from H. insolens was unexpectedly more active (145%) than other known cellulases. The applicant further contended that because all sequences of claim 1 were closely related, the surprising results obtained for the EGV could be reasonably extrapolated to all other sequences.[278] However, the Board found that these properties had not been substantiated over the whole claimed scope through sufficient experimental evidence that could have withstood critical scrutiny.[279] Consequently, the Board concluded the inventive step requirement was *not* fulfilled by claim1 in the main request.[280]

Despite this – at least for the appellant - negative result, it can nevertheless be concluded from T 1336/04 that as long as the solution to a certain problem is plausibly disclosed in the patent application, even unexpected advantageous properties can principally still be substantiated by post-filing data. Yet, this decision also indicates that it is then of crucial importance for the success of the application that such data is made available for critical scrutiny over the whole claimed scope. In other words, a plausible technical effect/surprising property which justifies acknowledging inventive step must be present "over the scope of the claim". Thus, T 1336/04 also demonstrates how the strict application of the inventive step requirement may contribute to achieving a balance between the technical contribution to the art made by the invention and the scope of the claim, which is considered to be one of the main features of a "high quality" patent.[281]

Only one week later Board 3.3.08 (chaired by Galligani) delivered its judgment in T 0604/04 "*PF4A receptors/Genentech*"[282]. The decision concerned a patentee's appeal against the Opposition Division's decision to maintain a patent in an amended and very limited form. The original patent comprised 22 claims that related, among other things, to novel DNA sequences and their expression products, which were identified and isolated with the help of the previously known IL 8 receptor-gene. The newly identified sequences encoded particular polypeptides, which allegedly functioned as receptors for highly potential proteins with a

---

[278] *Id.* at para 17 and XIII.

[279] *Id.* at paras 17-20.

[280] *Id.* at para 21 (for similar reasons, i.e. since claim 1 did mot meet the inventive step requirements under Art. 56 EC, the Board then also rejected the first and second auxiliary requests in para 23-25 of the judgment).

[281] In that regard *see further* case T 0665/05 "*modified HSV/ARCH*" (10 October 2006 – Board 3.3.08 - Galligani) (Like in case T 1336/04 the Board first distinguished the present case from the facts in T 1329/04 and concluded that the plausibility test was basically fulfilled; see para. 16: "There is a fundamental difference between this earlier case and the present one, namely that since the then claimed compound had not been described in the prior art, the plausibility of it being what was claimed must entirely rely on evidence provided in the application. In contrast, in the present case, the skilled person knew of the γ134.5 minus mutant from the prior art and, in particular, that its inoculation in a cell line of tumoral origin induced cessation of protein synthesis, this mechanism being confirmed and somewhat extended in the patent in suit." Then, however, the Board underlined at para 19 that in the present case the inventive step derives from the fact that non-obvious consequences were drawn from a specific effect and concerning this effect (i.e. on tumors in the central nervous system). Yet, in the absence of any further evidence the potential usefulness of the γ134.5 minus mutant *for treating tumors in general* remained in the view of the Board *a mere assumption.* In the light of these circumstances the Board held at para 20 "In accordance with the principles expressed in the case law (eg. T 939/92 and T 338/97 supra) that a technical effect which justifies acknowledging inventive step must be present "over the scope of the claim" and that there must be a balance between the technical contribution to the art made by the invention and the scope of the claim, the conclusion is reached that the claim of the main request which encompasses the use of the γ134.5 mutant for the manufacture of a medicament for treating tumorgenic diseases *in general* does not fulfill the requirements of Article 56 EPC whereas the claim of the first auxiliary request which is limited to the treatment of the tumors in the central nervous system does." Consequently, the Board concluded in para.24 that the main request is rejected under Art. 56, while inventive step was acknowledges for the first auxiliary request).

[282] Case T 604/04 *"PF4A receptors/GENENTECH"* (16.03.2006).

wide range of pharmaceutical applications – the so called PF4A-superfamily of cytokines. In support of this assertion, one of the patentee's chief arguments was that the claimed (receptor-) polypeptides were structurally similar to the previously known receptor for the IL-8 cytokine, which was known to belong to the PF4A-family. The Opposition Division decided, however, to reject all patent claims that related directly or indirectly to the novel IL-8 related receptor-polypeptides, as well as to the corresponding gene sequences. It held that cloning the DNA encoding these polypeptides was, due to the well-developed prior art on the cloning and expression of the known IL 8 receptor-gene, an obvious task. Moreover, the Opposition Division found that the applicant failed to disclose sufficient experimental evidence in the patent and, therefore, failed to show that the the polypeptides themselves had technically useful properties, or a credible function.[283] This was partly due to lack of any identifiable specific ligands to the claimed receptors. On appeal the Board's assessment focused in particular on the following controversial claims:

> (1) An isolated platelet factor 4 superfamily receptor (PF4AR) polypeptide having at least an 85% amino acid sequence homology with the translated amino acid sequence of figures 2, 4 or 5. (2) An isolated PF4AR polypeptide wherein the nucleic acid encoding the PF4AR polypeptide hybridizes with the complement of the nucleic acid encoding the polypeptide of figures 4 or 5 under high stringency conditions. (17) A monoclonal antibody that is capable of specifically binding the PF4AR polypeptide according to any one of claims 1 to 5. (21) A composition comprising the monoclonal antibody of any one of claims 17 to 20 and a pharmaceutically acceptable carrier. (22) A monoclonal antibody of any one of claims 17 to 20 for use in therapy or diagnosis.[284]

First, the Board summarized the closest prior art reference (document 2) which described the cloning of the IL-8 receptor gene, as well as the structure and functional expression of the encoded IL-8 receptor. On the basis of a comparison between the IL-8 receptor sequence and those of two other neutrophil chemoattractants, it was suggested that the IL-8 receptor belongs to the subfamily of related G protein-coupled receptors, which transduce signals for the IL-8 family of pro-inflammatory cytokines.[285] Starting from the closest prior art, Board 3.3.08 then defined the technical problem as pursuing the characterization of further receptors interacting with members of the PF4A family of cytokines.[286] Noting that the solution provided relates to the two polypeptides mentioned above, the Board subsequently checked whether this technical problem was actually solved according to the plausibility test approach taken in T 1329/04.[287] In doing so, it interestingly had to deal with facts that were rather similar to those in T 1329/04: The encoded amino acid sequences of the invention had a sequence identity of only 34% and 38% with the known IL-8 receptor (in T 1329/04, the identity was 34%). However, the Board managed to identify crucial distinguishing aspects which related to the fact that in the present case no significant structural inconsistency existed, such as the absence of a typical cysteine residue, which the person skilled in the art would have expected. The Board therefore held, in contrast to T 1329/04 and despite the fact that the application as filed did neither disclose the ligands of the

---

[283] *Id.* at III (adding that the OD had referred to R. 23 e (3) EPC and recital 23 of the EC Biotech Directive).

[284] Moreover, the Board considered claims 10–13, which related to nucleic acids and an expression vector encoding/comprising the sequence of the PF4AR polypeptide of any one of the preceding claims.

[285] *Id.* at para 3 (Of note: In the decision it is sometimes also referred to chemokines which are a family of small cytokines. The interleukin-8 protein encoded by the IL- 8 gene is a member of the CXC chemokine family).

[286] *Id.* at para 4.

[287] *Id.* at para 5 ("The solution provided is the two polypeptides of Figures 4 and 5. The first question which arises is whether or not these are bona fide solutions to the above defined problem. In accordance with the case law (T 1329/04 of 28 June 2005), 'the definition of an invention as being a contribution to the art, i.e. as solving a technical problem and not merely putting forward one requires that it is at least made plausible by the disclosure in the application that its teaching solves indeed the problem it purports to solve'.").

claimed polypeptides, nor any further convincing experimental data clearly supporting the hypothetical function, that the specific structural features of the sequences claimed in this case provided a plausible basis for the asserted function.[288] It summarized the situation as follows:

> 7. In this context, it is worth noticing that the situation is different from that encountered in the decision T 1329/04 (supra) where it was not accepted that the polypeptide SEQ ID No. 3 then claimed was a member of the TGF-β superfamily. In this earlier case, in addition to the fact that the polypeptide had not been shown to have any function, its structure did not conform to that expected from members of this family and the expected sequence homology to previous members of the family was not present.

Having concluded that the plausibility test was fulfilled, the Board then examined whether the claimed receptor polypeptides were also inventive.[289] In that context the Board first mentioned that the prior art disclosed a straightforward and successful method for the isolation of the IL-8 receptor and that the obvious way for the skilled person seeking to pursue the characterization of further receptors interacting with members of the PF4A family of cytokines would have been to follow the same method.[290]

However, the Board then underlined that the appellant followed a different procedure, which besides providing the possibility of isolating receptors irrespective of the proteins they were receptor for, was undoubtedly unexpected and full of uncertainties. The Board further emphasized that the appellant could only isolate two relevant molecules in the patent claims because he chose this different method, and that, therefore, inventive skills were exercised when isolating the claimed polypeptides. Consequently, the Board acknowledged that Art. 56 EPC was met.[291]

This case indicated once more that the same Board 3.3.08, which decided 1329/04, is still well prepared to conduct a critical and differentiating assessment of the various circumstances that surround each case. It would still accept that a fully consistent hypothetical teaching may amount to the disclosure of a complete invention that is open to the assessment of the most central patentability requirements, such as inventive step.[292]

---

[288] *Id.* at para 6 (adding: "For this reason, there is no absolute certainty that the polypeptides of Figures 4 and 5 are receptors for members of the PF4A family of cytokines - to which IL-8 belongs -.Yet, in the board's judgment, the above mentioned structural features make it plausible that this is indeed the case.").

[289] *Id.* at para 8 ("Having concluded in the affirmative as regard the plausibility that the molecules of Figures 4 and 5 are receptors for members of the IL-8 family of cytokines, the second question to be answered is whether or not they may be considered inventive.").

[290] *Id.* at para 9 ("Document (2) discloses a straightforward and successful method for the isolation of the IL-8 receptor, namely by using an expression cloning strategy.... Document (22), a review reflecting the common general knowledge on chemokines at the filing date teaches that numerous such molecules had already been identified ....The obvious way for the skilled person to solve the above mentioned problem of finding the receptors for chemokines would, thus, have been to proceed as in document (2), using radiolabelled derivatives of the chemokine of interest to identify which recombinant clones would bind to it; i.e., which recombinant clones expressed the corresponding receptor.").

[291] *Id.* at para 9 ("The appellant chose to proceed differently; it used IL-8 cDNA for probing under low stringency conditions cDNA libraries made from cells for which IL-8 was a chemoattractant.... In doing so, it provided the possibility of isolating receptors irrespective of the proteins they were receptor for. This course of action was undoubtedly unexpected and, beside, it was fraught with uncertainties given that low stringency conditions of hybridization might result in the isolation of cDNA artifacts. Had this different method not been chosen instead of the expression cloning strategy, the two molecules of Figures 4 and 5 would not have been isolated. Thus, inventive skills were exercised when isolating the claimed polypeptides which imply that they are patentable providing that they fulfill the further requirements for patentability.").

[292] Although not the focus of this paper, it should be mentioned that this decision also entailed interesting results concerning the industrial application (Art. 57 EPC) and sufficient disclosure requirements (Art. 83 EPC). In para 13 for example, the Board concluded that, in the absence of any characterization of its ligands (i.e. to the claimed PF4 receptor), its function at best remained incompletely understood. The Board then referred to the

More recently, it was further indicated in the previously mentioned T 1396/06 *"HLA binding peptides / EPIMMUNE"*[293] that even the other "biotech" Board of Appeal (3.3.04, chaired by Kinkeldey) is now also applying, or at least referring to, the plausibility principles that were developed in T 1329/04 and T 1336/04. As explained above, the invention at issue concerned immunogenic peptides of particular amino acid sequences, compositions containing the same, as well as the use of the peptides in medicine. While the broad claims in the main request, as well as claims in the first to fifth auxiliary requests had been rejected for lack of inventive step for the reasons discussed above,[294] the Board reached a different conclusion with respect to the plausibility and inventiveness of the *sixth auxiliary request*, in which ten claims were restricted to an immunogenic peptide *consisting of* one specific amino acid sequence (i.e. SEQ ID NO 101) with specific properties that suggested its use in HIV treatment.

The Board first found the closest prior art to be represented by document (1), disclosing the identification and isolation of immunogenic peptides specifically binding to HLA-A2.1. It then identified the problem underlying the subject-matter according to claim 1 of the sixth auxiliary request to lie in the provision of an immunogenic peptide with a high binding affinity for HLA-A3.2 for use as a vaccine to treat HIV infection.[295] Next, the Board emphasized that although the application as published disclosed that the claimed peptide's binding affinity for HLA-A3 was sufficiently high to be capable of eliciting a CTL-immune response, the actual data proving the positive peptide response caused by the peptide in PBMCs of HIV infected patients was first submitted in document (6), which was published after the publication of the present application.[296]

Thus, the Board first had to determine whether the technical problem defined above was actually solved by the subject-matter of claim 1 at the relevant date, and in particular, whether in reaching this decision it could take into account the post-published evidence. The Board then recited the principles laid down in the case law of the other "biotech"- Board 3.3.08, i.e. the previously described decisions in T 1329/04, where it was held that supplementary post-published evidence may not serve as the sole basis for establishing that the technical problem is solved, and T 1336/04, which clarified that, where the quality of evidence provided in the respective patent was such that the claimed invention was considered to be a *bona fide* solution to the identified problem, the disclosure in a post-

---

strict criteria applied in T 870/04 but this time it saw the industrial applicability requirement as fulfilled; *see id.* at para 18 (holding: "It is clear... that chemokines as a family were considered not only to be interesting in fundamental research but also as important for the pharmaceutical industry irrespective of whether or not their role had been clearly defined. It follows that their receptors must have been considered equally important since the mode of action of chemokines is through their receptors. It is, thus, reasonable to conclude that the polypeptides... which exhibit the characteristics of receptors of members of the PF4A family of cytokines would have been regarded as important to the pharmaceutical industry; i.e., that industrial applicability may be acknowledged.") Considering the sufficient disclosure requirement at paras 20-28, the Board acknowledged that this requirement was fulfilled by the receptor-polypeptides, *but* - rather interestingly - it reached, despite the general acknowledgment of industrial applicability of the claimed polypeptides, a different conclusion for the monoclonal antibodies in claim 21-22. More specifically, the Board found at para. 25 that, "(t)he mere disclosure of a monoclonal antibody against the polypeptides of Figure 4 or 5 without identifying a diseased state caused by the "misfunctioning" of these polypeptides is not sufficient to acknowledge a use in therapy for the monoclonal antibody. For these reasons, it is concluded that the requirements of Article 83 EPC are not fulfilled in respect of... claims 21 and 22."

[293] Case T 1396/06 *"HLA Binding Peptides/EPIMMUNE"* (31.05.2007 – Board 3.3.04), *see also supra* note 167.

[294] As for the main request and the 1st - 5th auxiliary request the Board decided that the provision of various immunogenic peptides specifically binding to HLA-A3.2 was in the light of the prior art routine and obvious.

[295] Case T 1396/06, *supra* note 293, at para 30.

[296] *Id.* at para 31.

published document may be accepted to support the asserted solution. Applying these principles to the fact of the case the Board held at paras 34-35:

> When evaluating the quality of evidence provided in the present application as published, the Board notices that the claimed peptide is shown there to contain an HLA-A3.2 specific motif and having a binding affinity for its specific MHC-allele which indicates its capacity to elicit a CTL response. Experimental data, contained in post-published document (6), actually showing the induction of this CTL response in PBMCs of HIV-infected patients, are considered to back up the findings of the patent application as published. 35. Considering decisions T 1329/04 and T 1336/04 (supra), the Board is convinced that the present circumstances are appropriate to take into account supplementary post-published document (6) when establishing whether the application solves indeed the problem it purports to solve. In the light of the disclosure in the application as published, which is backed up by post-published document (6), the Board is satisfied that the problem as determined in point (30) above is solved by the subject-matter of the claims of the sixth auxiliary request.

Thus, the Board focused on the fact that the claimed peptides high binding affinity for HL-A3.3 was already disclosed in the patent application, which plausibly indicated that the peptide would indeed be capable of inducing an immune response. Under these circumstances the Board found it appropriate to take account of post-published evidence that supported the assertion in the patent application.

Concerning the remaining question of whether the accepted solution to the problem involves an inventive step, the Board distinguished the present situation from its findings with regard to the main request and the first to fifth auxiliary requests. The Board found that although it was in the light of the combined prior art obvious to produce immunogenic peptides specifically binding to HLA-A3.2, this would not allow to draw a conclusion concerning the expectation of success to isolate a specific peptide (SEQ ID NO 101) for the defined use as vaccine for treating HIV-infection. Thus, the Board based the inventiveness of the sixth auxiliary request on surprising elements related to its specific use, holding at para 37:

> The Board does not doubt that a skilled person, knowing the HLA-A3 motif of document (4) and trying to solve the problem underlying the present invention according to claim 1 of the sixth auxiliary request, would make use of the isolation-, purification-, sequencing- and screening-method disclosed in document (1). This method will, by using the appropriate peptide motif, result in the provision of immunogenic peptides specific for the desired MHC-molecule in an obvious way, *but* it does not allow to draw a conclusion concerning the expectation of success to isolate a specific peptide (SEQ ID NO 101) for the defined use as vaccine to treat HIV-infection. In this situation it is not the theoretical possibility to isolate a substance by applying a known method, but the actual provision of one specific peptide for a defined use, not disclosed in the prior art, which establishes elements of surprise justifying acknowledgement of an inventive step.

Consequently, the Board decided that the sixth auxiliary claim overcame the objections on inventive step. After determining further that the requirements of article 83 EPC were fulfilled[297], the Board remitted the case back to the department of first instance with an order to grant a patent on the basis of the sixth auxiliary request.

---

[297] Of note: The Board also held that whilst Article 83 EPC requires an application to disclose the suitability of the product to be manufactured for the claimed therapeutic application, post-published evidence such as clinical trials data can be taken into account to back up the findings in the patent application, provided the application provides some information, such as e.g. experimental tests. The Board considered that the appellant's application contained sufficient information from which it could be determined that the claimed peptide would act in the manner required (it was isolated from an HIV strain, contained a motif specific to the required allele and demonstrated sufficient binding affinity to elicit an immune response). In that regard Board 3.3.04 further confirmed decision T 609/02 where the Board 3.3.08 had taken into account the intrinsic difficulties for a

Only two weeks later the same Board 3.3.04, chaired by Kinkeldey, had to consider a rather similar situation in T 433/05 *"Fusion Peptide Inhibitors/CONJUCHEM"*[298]. This time, the patent at issue - or rather the new main request submitted during the oral proceedings - related to specifically modified anti-viral and antifusogenic peptides and claimed their use in the manufacture of a medicament for preventing and/or treating viral infection.[299] As for the inventive step examination, the Board and the concerned parties considered the closest state of the art to be represented by a document (1), which disclosed anti-viral and antifusogenic peptides including a wide range of peptides (sequence 1- 86) specifically mentioned in the present set of claims. This document also referred to the use of these peptides for the prevention and/or treatment of viral infections and mentioned that the peptides may include modifications, as well as additional amino- and carboxy-groups.[300] Due to various biochemical factors, however, the in vivo stability of these peptides was unsatisfactory.[301]

In light of this prior art, the Board identified the problem underlying the new main request in the contested patent to relate to the provision of medicaments for the prevention and/or treatment of viral infections *having increased in vivo stability whilst at the same time retaining their antifusogenic activity*. The Board also held that the subject-matter of the relevant claims could be distinguished from the closest prior art, because the anti-viral and antifusogenic peptides are coupled to a maleimide group, which is reactive to a thiol group on serum albumin to form a *stable* covalent bond.[302] However, the Board then also pointed out, that it could only be proved with experimental data after the filing date, that this specific modification would result in additional positive effects, which could be useful for further development of therapeutic (i.e. through the maintenance of the therapeutic activity in combination with the extended in vivo half-life).[303]

Thus, as in its former decision in T 1396/06, the Board *first* had to determine whether the technical problem defined above had indeed been solved by the claimed invention at the relevant date, and whether the post-published evidence could be considered in this context. As in T 1396/06, the Board then recited the principles established by Board 3.3.08 in T 1329/04 and T 1336/04. Considering those principles in light of the present case, the Board began by reminding that all specific peptides used in the manufacture of medicaments according to the claims were known from the prior art in their unmodified form [document (1)], where also their anti-viral and antifusogenic activity is disclosed.[304] Then the Board continued:

---

compound to be officially certified as a drug including several years of tests and very high development costs. In T 609/02 it was therefore accepted that for a sufficient disclosure of a therapeutic application in a patent/patent application, it is not always necessary that results of clinical trials are provided at the relevant date, but that it is required that the patent/patent application provides some information in the form of, for example, experimental tests, to the avail that the claimed compound has a direct effect on a metabolic mechanism specifically involved in the disease (*cf.* para 6 of T 609/02 and para 39 of T 1396/06).

[298] Case T 433/05 *"Fusion Peptide Inhibitors/CONJUCHEM"* (14.07.2007 – Board 3.3.04), *available at* http://legal.european-patent-office.org/dg3/pdf/t050433eu1.pdf .

[299] The appeal was lodged by the Patent Proprietor (Appellant) against the decision of the Opposition Division, whereby the European patent No. 1 179 012 was revoked pursuant to Article 102(1) EPC. The Appellant requested that the decision under appeal be set aside and the patent be maintained on the basis of the new main request submitted during the oral proceedings.

[300] *Id.* at para 5.

[301] *Id.* at para VII.

[302] *Id.* at para 7.

[303] *Id.* at para 8 (stating: "After the filing date the Appellant has submitted document (18), consisting of Annexes I, II and III, which contains experimental data showing that DP178 peptides, modified as described in present claim 1, had extended in vivo half-life and displayed anti-viral and antifusogenic activity").

[304] *Id.* at para 11.

> 11. When evaluating the quality of evidence provided in the patent in suit (and in the application as published), the Board notices that it contains thirty examples concerned with the preparation of modified peptides according to the invention. The use of the modified anti-viral and antifusogenic peptides is described on page 17, the different ways of administration of the modified peptides to patients in need thereof on pages 17 and 18 of the patent. Bonding of the peptides to long-living blood components, like serum albumin, is said to extend the activity of the peptides (page 18, lines 7 to 11), and a method for detecting the extended presence of the modified peptides in a patient's blood by a specific immunoassay is described on pages 18 and 19.

Without any additional comments on the complete absence of any experimental "wet biology" or "in silicio" evidence at the relevant date which would have demonstrated, or at least indicated (*cf.* T 1396/06 & T 604), that the modifications actually increased in vivo stability of the peptides whilst retaining their therapeutic effect, the Board concluded that it was convinced that the current circumstances were appropriate to take into account the support of supplementary post-published evidence on such effects when establishing whether the application indeed solved the problem it purported to solve. In the light of these findings, the Board was satisfied that the problem was solved by the subject matter claimed.[305]

Concerning the final and crucial question of whether this "plausible" solution to the problem included an inventive step, the appellant argued that a skilled person, bearing in mind the mechanisms by which antifusogenic peptides act and expecting inherent scientific problems, would not have considered to combine the teachings in the prior art in a way that would have led him to follow the same modification procedure that the appellant had applied. Moreover, the appellant highlighted that the skilled person would at the relevant date have been aware of a plethora of alternative methods to increase the in vivo half life of therapeutically active peptides, which were all more promising than the method followed by the applicant.[306] However, the respondent denied that a skilled artisan would have expected particular problems when combining the prior art at issue, and would therefore not necessarily have preferred to follow other routes to increase the in vivo half life.[307]

Addressing these arguments, the Board first pointed out that the situation in the present case was *not* to be regarded as a so called "one way street" solution, because the skilled person would have been aware of a variety of alternative procedures to solve the identified problem.[308] Regarding the divergent views on the question of whether the prior art actually "taught away" from the modification procedure followed by the applicant, or at least hinted towards potential problems, the Board noted that although it could not be derived with certainty from the prior art that such problems would indeed occur, the prior art at least pointed to problems which may result.[309] The Board found in particular that a skilled person, being aware of more promising methods, would have taken these hints into consideration. It further emphasized that no other prior art document would have convinced the skilled person that the expectation of problems, as hinted at in the prior art, was unfounded. The Board therefore decided that:

---

[305] *Id.* at para 12.

[306] *Id.* at paras 15-16 (arguing that it could be derived from the prior art that conjugating of an antifusogenic peptide to a moiety of about the size of albumin will inevitably lead to steric hindrance problems as a result of the very limited three dimensional space at the environment in which an antifusogenic peptide must be active).

[307] *Id.* at paras 17-20 (contesting the appellants interpretation of the prior art and referring to further documents).

[308] *Id.* at para 25 (holding: "to summarise, the skilled person trying to solve the problem underlying the patent in suit, namely to provide medicaments for the prevention and/or treatment of viral infections having increased in vivo stability whilst at the same time retaining their antifusogenic activity, was aware of a number of alternative procedures to increase the in vivo therapeutic halflife of the antifusogenic peptides known from document (1) (see point (16) above). The situation... cannot be compared with what is called a 'oneway- street' situation.").

[309] *Id.* at para 26 (The problems related to the the high mass of the carrier, which was 90% of the conjugate).

> [a] skilled person at the relevant date of the present invention, would not have considered to conjugate antifusogenic peptides via a maleimide group, either with or without a short linker, to serum albumin, a protein with a molecular mass of 66 kDa, in order to provide medicaments for the prevention and/or treatment of viral infections having increased in vivo stability whilst at the same time retaining their antifusogenic activity.[310]

Consequently, the Board held that the claims in the appellant's new main request could not be derived in an obvious way from the combination of the prior art and therefore involved an inventive step in accordance with article 56 EPC. After further concluding that the main request was also sufficiently disclosed in line with Article 83 EPC[311], the Board set the appealed decision aside and ordered the first instance department to maintain the patent on the basis of the new main request.

4. Discussion: How much is enough?

Both, the rewards for acquiring a dominant biopharmaceutical patent, and the costs of subsequently developing a properly approved drug with the protected invention, can be enormous. Thus, applicants often race to be the 'first out of the blocks' when seeking patents on a promising technology. While it has always been considered wise to submit data that support the inventive concept of the concerned invention in the patent application, applicants have in the past often relied on the fact that the European Patent Convention does not explicitly require the presence of experimental data or worked examples at the date of the application.[312]

Yet, the above described recent decisions by the European Patent Office (EPO) Boards of Appeal demonstrate that those who submit their application too early and do not submit sufficiently coherent and reliable data face a considerable risk of having their "implausible" patent applications rejected or their patents invalidated for *inter alia* lack of inventive step. Moreover, the previous analysis has shown that once an application has been held to be "implausible", it may be rejected even if post-published evidence demonstrates that the initial assertions were correct. In that context, the Board of Appeal initially appeared to have taken an overly restrictive position in determining when a disclosed DNA-related invention was sufficiently complete to allow an assessment of the further patentability requirements. This restrictive position, which might presumably be regarded as an early legal reaction to the problems that were partly caused by the revolutionary mass sequencing

---

[310] *Id.* at para 27.

[311] *Id.* at paras 28-29 (Of note: The Board reached its conclusion with regard to article 83 EPC on similar grounds as in T 1396/06, and referred to the same case law. First, it underlined that the application must disclose the suitability of the product to be manufactured for the claimed therapeutic application, but that this would not necessarily require the provision of clinical trials results at the relevant date, provided that the patent/patent application provides some information to the avail that the claimed compound has a direct effect on a mechanism involved in a disease. Here, the Board found in particular that the prior art disclosed in the patent application provided sufficient information on such effects for unmodified peptides, although – in contrast to T 1396/06 – not one single experiment pointing towards the more specific asserted effect of the claimed modifications was disclosed, i.e. with regard to the *increased in vivo stability and the maintenance of the therapeutic effect.* The Board also considered that the description of the medical use of the peptides and the different ways of their administration to patients was – together with the description of a specific method for detecting the presence of the modified peptides in a patient's blood - included in the patent application. Under these circumstances the Board was willing to take into account the post-published experimental evidence supporting the effect of the modifications, and decided that a skilled person could have carried out the invention by following the disclosure).

[312] *See* Connor McConchie & Charles Harding, *How much is enough?*, World Intellectual Property Review, 48-52 (Nov./Dec. 2008), *available at* http://67.19.80.66/worldipreview/index.aspx?issue=TWIPR/issue04 (last visit: 10 July 2009) (adding that neither the UK Patents Act does require such data).

approaches, is reflected by the "plausibility test" as it was established in T 1329/04.[313] It also appeared as if the Examining Division had generally adopted an overly strict standard in the wake of this decision.[314]

In the last years, however, the Board seems to have refined and further developed its approach, which resulted in a more balanced and pragmatic solution to the problem. The further development of the legal principles resulted in more differentiated case-by-case results that *inter alia* seem to take into account the fierce international competition in each specific field of technology. In addition, the Board apears to pay proper attention to the maturity and predictability of the art that relates to the claimed invention, or even further conditions that might influence the plausibility of asserted effects. Yet, it also became evident that the necessary balancing of objective aspects, i.e. the specific facts in each case, and subjective aspects, i.e what is considered to be plausible to a person skilled in the art, leads to a rather complex legal situation.

It is, therefore, not surprising that a considerable legal uncertainty still remains: Consider an applicant for a biopharmaceutical patent application relating to a new compound, new uses and formulations of known compounds, polymorphs or the similar. Such an applicant may rely on essential assertions of physical, biological or further effects to prove an inventive step. In such cases, the applicant will face a difficult decision: Either you could file the application without any, or only vague, evidence of a technical effect and risk the EPO refusing the application for *inter alia* lack of inventive step, or you delay the filing until some evidence of efficacy is obtained but risk in the meantime that your invention is anticipated.[315] Moreover, it might be a bad idea to provide too much information about the prior art in order to render the asserted functions plausible, when the same evidence might indicate a "reasonable expectation of success" and thus would ultimately render the claimed invention obvious. Consequently, the most crucial question for patent applicants in this highly competitive field is: "What is the minimum amount of information that a patent application must provide at the filing date in order to obtain a valid legal monopoly?"

The answer to this question is not simple and will depend very much on the facts of each case. The necessary amount of data, if any at all, may differ depending on a number of factors, including the nature of the invention itself and the common general knowledge in the technical field. The amount of data required might also differ for the various patentability criteria that must be satisfied in order to achieve grant.[316]

---

[313] Jaenichen, *supra* note 245, at 13.

[314] *See* Hendrik Wichmann & Fritz Lahrtz , *Pitfalls and Opportunities in Biotech and Pharma Patenting*, Managing Intellectual Property, 89, 89 (4/2008) (contending that "the two Boards of Appeal appear to decide the issue of the necessity of experimental evidence in the original application on a case-by-case basis, wherein one Board seems to be stricter than the other." With reference to the pending case T 1642/07 (currently before Board 3.3.04) it is further pointed out that "the Examining Divisions seem to adopt the stricter standards set by the Board 3.3.08 in that many applications are now objected to or even rejected for lack of inventive step because of an alleged absence of experimental evidence.").

[315] *See* Elend & Johnson, *supra* note 233, at 14.

[316] *See* McConchie & Harding, *supra* note 312, at 49; *see also* White, *supra* note 265, at 641 (pointing out with regard to the relationship between "sufficient disclosure" and "inventive step" under the "plausibility-test": "Even if the requirements for sufficient disclosure are met, experimental evidence may still be required to show that an 'invention' has been made in comparison to the prior art. It is not possible to use post-filing date experiments to show that an 'invention' solves the technical problem it purports to solve in comparison with the prior art if this is not "at least plausible.") In that regard, it might be argued that the inventive step examination under the "plausibility-test" could in some cases result in adding a further requirement for patentability which goes beyond the industrial application requirement pursuant to Art. 57, or the sufficient disclosure requirement under article 83. As it has been indicated above (*see supra* note 46), it has been admonished in legal literature that such a result would have to be avoided. Consequently, such (potential) results appear to be rather debatable.

Although the wide range of diverse facts that might be considered by the Board in each and every case does not allow one to draw a clear line between the decisions as to when supplementary post-published evidence will or will not be allowed and what is exactly meant by "plausible", the principles that could be derived from the decisions mentioned above nevertheless provided basic guidelines. More specifically, it appears from the case law of the Board of Appeal that the success of a patent application and later submitted evidence is more unlikely under the following circumstances: 1) where the application as filed discloses no function at all, (2) where the function inhabits a particular application that was not disclosed with sufficient specificity at the date of the application, (3) where the evidence submitted in the application apparently contradicts itself, *or* (4) where the disclosed asserted function - which might depend on the affiliation of a compound to a specific superfamily – would, in the absence of any further evidence, stand in conflict with the knowledge of the prior art, so that the skilled reader would have serious doubts that the alleged effects will in fact be displayed.

On the other hand, where at least some *credible* evidence of efficacy exists in the application as filed, supplementary evidence might still be allowed. Under certain circumstances such evidence may even relate to "in silicio" experiments and/or substances similar to but not actually falling within the claims. In that case, however, an applicant must show that the functional predictions are more than an unsubstantiated speculation, and that the assumptions are consistent and convincing. In particular, the Board's case law indicates that where an educated guess was made and neither any evidence on file, nor any other circumstance suggests that this guess is wrong, then post-published evidence that confirms the preliminary finding and actually supports the conclusion cannot be ignored. This was for example demonstrated by T 604/04, where, although only sequence alignments were disclosed but no "wet biology" data, a sufficiently consistent structural identification and allocation to an existing group of proteins could be presented (i.e. in contrast to the missing cysteine residue in T 1329/04). Under these conditions, later experimental evidence confirming the hypothetically disclosed function was permissibly considered.[317]

Furthermore, it appears as if Board 3.3.04 followed a rather liberal approach when it accepted post-published evidence in its inventive step assessment in T 433/05.[318] It should be emphasized that in this case the application included *no* specific evidence supporting the claimed technical effect (or the actual contribution to the state of the art), which related to the extended *in vivo* stability of therapeutically active proteins. The application merely described the preparation and administration of the modified proteins and disclosed a method for detecting and monitoring the extended presence in the blood of patients. Thus, it only provided the tools for acquiring further experimental evidence concerning a) their extended *in*

---

[317] *See* Jaenichen , *supra* note 313, at 13; *see also* case T 604/04, *supra* note 282, at para 24.

[318] This estimation is shared by Wichmann & Lahrtz, *supra* note 314, at 89. Interesting in this regard is also the position taken by Board 3.3.04 in case T 903/05 "*Telomerase peptides/GEMVAX*" (20 August 2007) when considering the right to priority under Art. 87 to 89 EPC for a selection invention. After having underlined the importance of following the principles that have been established by G2/98 "Requirement for claiming priority of the 'same' invention" (31 May 2009) (para 9), the Board confirmed the claimed priority date for the (DNA – related) patent in suit and reasoned as follows: "11. Since the enablement of the disclosure of the priority document has explicitly not been challenged by Appellant II, the Board does not consider it appropriate to doubt that the priority document discloses the claimed invention in an enabling way. Beyond the issue of enablement, the Board sees no legal basis for imposing additional criteria such as the presence of experimental data in the priority document which make plausible that the invention would work. The Board is furthermore convinced that the experimental data which are present in the patent and not in the priority document do not change the nature of the invention disclosed. 12. Appellant II submitted that in view of decision T 1329/04 of 28 June 2005, it would be necessary that the priority document contained experimental data which made plausible that the invention now claimed worked. However, said decision is concerned with the question of inventive step and is therefore not relevant for the present issue of entitlement to priority."

vivo half-life and b) the maintenance of their therapeutic activity. With regard to the therapeutic effect, the application relied on prior art that clearly showed the unmodified proteins to be therapeutically active and suggested that they could, or should, be modified for drug development. However, the prior art also indicated that the skilled person would have doubted that the method as applied by the applicant would be successful, which ultimately provided the basis for the inventiveness of the solution. In light of this skepticism, the Board's decision that the initial application was plausible and it's acceptance of post-published evidence confirming the claimed effect was rather remarkable. This liberal attitude may nevertheless be explained, and probably also justified, by a variety of factors, such as the well-developed prior art, the high competition in the therapeutic field, the specific competence of the inventor, and, presumably, also the enormous significance of the potential drug at issue for AIDS treatment. In other words, the invention was utterly beneficial to millions of patients and development of a therapy was urgently needed with patent rights providing the economic ratio for companies to conduct expensive and risky clinical trials.[319]

While some uncertainty persists and it will hence remain important to carefully monitor how EPO case law will evolve in detail, the most recent case law developments seem nevertheless to have eased the worries of many practitioners. The combined reading of these cases reveals that the "performable is sufficient" principle is still applicable. The "performed required" standard seems to be reserved for exceptional cases in which the *in silicio* or *in vitro* analysis produces structural inconsistencies that would be considered relevant to the skilled worker.[320] Moreover, it was demonstrated by the decision in T 433/05 that the EPO might under extraordinary circumstances still allow supplementary evidence even where evidence of efficacy is completely absent in the application as filed. Although several of the Board of Appeal's decisions require at least some convincing evidence of efficacy in every application for an invention to be "plausible", this approach does not appear to be universally adopted in cases concerning significant inventions that stem from a field with a well-developed prior art and common general knowledge. As it will further be shown in Part II, a rather liberal approach allowing a more patent-friendly interpretation of the plausibility standard has now also emerged in seminal national case law, as it is demonstrated by the

[319]Another question is of course if the clinical trials for such important drugs would necessarily have to be conducted by patent- seeking companies; *see* the discussion in part II.

[320] *See* Jaenichen, *supra* note 313, at 13 (proposing a two-step approach for assessment of whether a disclosed technical teaching amounts to the disclosure of a complete invention, including two steps. The first concerns the structural expectation in the prior art and the definition of the structural target. Here, it would first be asked if the disclosure of the patent application consistently satisfies the structural expectation of a person skilled in the art and, thus, meets the defined target. If this is not the case the application would have to be refused. If the structural expectation requirement is fulfilled the application would still have to meet the requirements on the second step, which, as it is proposed by Jaenichen, relates to the functional expectation in the prior art and the definition of the functional target. It involves the following question: Does the disclosure of the patent application, that survived question 1, optionally in combination with later produced experimental evidence supporting any disclosed function, satisfy the functional expectation and, thus, meet the defined functional target? Only if the answer is yes, the invention would be patentable); *see also* David Rogers, *EPO takes pragmatic view*, 2 J. I. P. LAW & PRAC. 1, 6–7 (2007). *See also* current EPO Examination Guidelines at C-VI, 5.3.5.: "Under certain circumstances [...] later filed examples or new effects, even if not allowed into the application, may nevertheless be taken into account by the examiner as evidence in support of the patentability of the claimed invention. For instance, an additional example may be accepted as evidence that the invention can be readily applied, on the basis of the information given in the originally filed application, over the whole field claimed..... Similarly a new effect [...] may be considered as evidence in support of inventive step, provided that this new effect is implied by or at least related to an effect disclosed in the originally filed application [...]."

recent UK House of Lords' decision in Angiotech.[321] In this case, a claim on a stent coated with a specific drug (taxol) was considered to be inventive despite the fact that the application as filed included *no* sufficient evidence demonstrating that the drug would actually exhibit the alleged efficacy in preventing restenosis when using the claimed modified stent. The applicant further failed to prove at the date of the application that the drug could be used despite the previous concerns about its toxity. The Court affirmed the patent on the basis that the invention was "performable" and that the solution to the identified problem was "plausibly" disclosed in light of prior art documents and the common general knowledge.[322]

Yet, the mere existence of substantial room for argumentative maneuver, particularly in fields with well-developed prior art and common general knowledge, cannot conceal the fact that the decisions discussed above have, in principle, applied a "high quality" threshold for acceptable evidence and have confirmed the plausibility test. As it was shown above this standard is now also readily applied by the Examining Divisions. Therefore it is important to point out, that it seems to be generally required for all patentability criteria that the application as filed contains sufficient information in order to ensure that the invention as defined in the claims is at least "plausible", without placing undue burden on the skilled person to confirm it. Thus, as a general rule, the provison of supporting data has become much more important for the success of patent applications.[323] This seems to be especially

---

[321] *See* UK House of Lords' in: *Conor Medsystems Incorporated v Angiotech Pharmaceuticals Inc. & others* 2008 UKHL 49; (2008) R.P.C. 28 (for a more detailed analysis of the various issues raised by this seminal decision *see* part II).

[322] *Id.* at para 36., *cf.* Elend & Johnson, *supra* note 233, at 14 (arguing that there is thus clear pressure on the EPO not to generally require that at least some evidence of efficacy must always be present in the application as filed. In the light of the prevailing uncertainty it is then further advised that: „As a general rule, however, unless the evidence of efficacy is already available or can be obtained particularly quickly, we would normally recommend filing a priority application at the earliest possible opportunity, especially in highly competitive fields. However it is of course prudent to try and include at least some evidence of efficacy (however slim) before the end of the priority year and at the latest in any subsequent patent application claiming priority from the initial application. In so doing, the applicant will then have captured the earliest possible protection in any subsequent patent application claiming priority from the initial application. In so doing, the applicant will then have captured the earliest possible priority date for his invention whilst also ensuring as a fall-back position that there is some evidence of efficacy in the application as filed, even if not in the initial priority application. (...) It is still very strongly arguable, particularly in view of the lack of any BoA decisions in the chemical or pharmaceutical sector considering T 1329/04, previous EPO practice in this regard, and the UK House of Lords judgment, that supplementary evidence of efficacy should be allowed before the EPO.").

[323] *See* Wichmann & Lahrtz, *supra* note 314, at 89 (concluding with regard to inventive step that "For patent practitioners, the most important effect of these decisions is that the date of filing has to be considered carefully. It is highly recommended that at least some early evidence is included in the application. An interesting though undecided issue is whether it is necessary to include the data in the priority application or whether it is enough to incorporate it in the subsequent (PCT) application. It seems best to include it in the priority application, but due to other constraints this may not always be feasible. In already pending applications, post-published data should always be submitted as further evidence in support of statements or (even better) data already presented in the application, so that the post-published data only represent additional proof that the problem has indeed been solved by the present application.") Concerning the sufficient disclosure requirement *see also* White,, *supra* note 265, at 641 (concluding that substantial insufficiency cannot be remedied by late-filed data, although such data could still be submitted to show that paper examples actually work or that the invention works over the whole range claimed (as long as one way of performing the inventions is adequately described). It is also emphasized that with certain inventions, notably those concerning therapeutics, the requirements for sufficient disclosure go beyond enabling skilled readers to "make and use" the invention. The application as filed must contain some evidence of therapeutic efficacy.) Concerning the UK *cf.* McConchie & Harding, *supra* note 312, at 51-52 (concluding after an analysis of *Conor Medsystems Incorporated v Angiotech Pharmaceuticals Incorporated & others* (2008) UKHL 49 and *Eli Lilly & Co. v Human Genome Sciences Inc.*, (2008) EWHC 1903 (Pat.), that "it is important to point out that, in all cases, the provision of supporting data in an application is invaluable. However, ... in some situations, time is of essence. In these situations, it appears that in order to

true for applications in unpredictable fields of technology with less-developed common general knowledge. Such a result also corresponds with the general policy goal of the EPO, i.e. to heighten the quality of patent applications and patents in order to make the granting procedure more efficient and to meet utilitarian goals by well-defined patent rights with an appropriate scope of protection.[324]

While these developments should be welcomed, it must, however, also be kept in mind that it will most likely become increasingly unproblematic for future patent applicants claiming DNA-related inventions to provide such "high quality" evidence for predicted functions. This presumption can be based on the rapid advances of the state of the art and the expansion of the common general knowledge, which renders biotechnology in general more predictable. Technological advances will, for example, allow applicants to submit more convincing computer-assisted educated guesses on DNA or protein functions or to base their technical conclusions on DNA sequence homologies to better known genes with a high probative value. Thus, the truly decisive question will have to be answered on the final step of the inventive step inquiry, or more specifically, when it has to be determinationed whether the plausible solution to the problem was indeed inventive. As it has been indicated above and will be discussed further below, this final question will in the light of recent technological advances presumably present an ever more serious hurdle for future applicants.

D. Preliminary evaluation

The previous analysis has shown that the EPO applies a rather flexible assessment of the inventive step requirement with regard to biopharmaceutical inventions and considers a great variety of factors on which an inventive step may be based. Generally, the inventive step of, for example, a DNA or protein-related invention can be based either on particular difficulties involved in the isolation procedure, an inventive selection or on secondary evidence, such as unexpected properties. In contrast to U.S. patent law prior to KSR, the EPO had never applied an overly rigid interpretation of the structural similarity doctrine in the context of DNA related inventions, as it had been previously established by the CAFC decision in *In re Deuel*[325] in the form of the strict the structural predictability approach, which had now been repudiated by *KSR* and *In re Kubin*.[326] While U.S. courts had since 1995 followed *In re Deuel* and had thus primarily concentrated on the different chemical structures of previously known amino acids and the corresponding DNA sequences, the EPO had instead continued to focus on the predictability of the isolation procedure and the "reasonable expectation of success" doctrine, as it had been previously applied in the earlier CAFC decisions in *In re O-Farrell* and *In re Vaek*.[327] Therefore, the EPO was in a better position to

---

secure a valid UK patent, sufficient information that satisfies as closely as possible the nine principles mentioned by Judge Kitchin is needed.).

[324] In its Annual Report 2008, the EPO has announced a portfolio of measures that will raise the bar on the quality of patents while improving efficiency in the granting process, the report is *available at* http://www.epo.org/about-us/office/annual-reports/20083df8.html. In the foreword to the report, the current EPO President Alison Brimelow says, "The EPO is devoting particular attention to further enhancing patent quality, which is also dependent on the quality of the applications that are filed." Further information is *available at* http://www.epo.org/topics/news/2009/20090424.html (last visits 10 December 2009). These developments are not only closely followed, but also welcomed by the European Commission, *see infra* note 346.

[325] *In re Deuel*, 51 F.3d 1552 (Fed. Cir. 1995) (Judge Lourie).

[326] For further detail, see part II.

[327] *See* Judge Rich in *In re O'Farrell*, 853 F.2d 894, where it was held that in the view of the prior art there was a "reasonable expectation of success," and, in particular, that obviousness does not require absolute predictability of success. For a different result under the same principles, *see In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). A more comprehensive discussion of these cases is provided by Minssen, *supra* note 14, at 112. *See*

more properly consider the obviousness of the isolation method that led to the disclosure of the claimed DNA sequence and could thus take duly into account technical developments.[328]

Although it might be argued, as we will see in Part II, that U.S. courts had already applied a rather flexible obviousness standard for pharmaceutical invention in the years prior to *KSR*,[329] it is also evident that *KSR* seems now to have brought the U.S. law of obviousness much closer to the current EPO approach. A more detailed analysis of the CAFC decision in *In re Kubin* in Part II, will further demonstrate that this is particularly true for DNA and protein- related inventions.[330] Consequently, the well-developed EPO case law on the "reasonable expectation of success" doctrine in biotechnology should become an interesting source of comparative inspiration for U.S. practitioners.[331] In that regard, it has to be particularly emphasized that the EPO's rather well-balanced interpretation of the "reasonable expectation of success" doctrine and the consideration of secondary evidence for many years had ensured that a biopharmaceutical invention was not necessarily held obvious just because it was "obvious to try".[332] Hence, patent applicants are still left with some leeway when arguing in favor of the inventiveness of a claimed invention. As it will be discussed further in Part II, post-KSR case law developments in the U.S. equally suggest that, although the obviousness requirement has become a much more difficult hurdle to overcome, patent applicants still seem to have significant leeway to argue for the non-obviousness of DNA or protein-related inventions. Yet, there also appeard to be a great risk that the "person of ordinary creativity, not an automation" and "common sense" standard that KSR established for the PHOSITA results in legal uncertainty. It may also lead to different results and perhaps a greater danger for hindsight decisions in the assessment of the capacity of the PHOSITA

---

also Judge Rich's opinion in *In re Papesch*, 315 F.2d 381 (C.C.P.A. 1963) (admonishing the USPTO to look beyond structure when analyzing the obviousness of a new chemical, directing attention to how the chemical works, rather than merely what it looks like).

[328] Krefft, *supra* note 171, at 146-49 & 154-57 (criticizing the very low inventive step threshold as it was established by *In re Deuel* and arguing that this decision had – unlike the EPO approach - not only "frozen in" the consideration of the state of the art, but also ignored that the structural similarity doctrine was misplaced in the DNA context due to the specific DNA-protein relationship.) *See also* his analysis concerning the consequences of the (formerly) different US and EPO approaches with regard to DNA fragments, such as ESTs and SNPs at 158-62.

[329] *Cf.* Rebecca Eisenberg, *Pharma's Nonobviousness Problem*, 12 LEWIS & CLARK L. REV., 375 - 430 (2008).

[330] *Id.*; *see also* Minssen, *supra* note 23, at 915 & 916; concerning German case law see also Peter Meier-Beck, , *Die Rechtsprechung des Bundesgerichtshofs zum Patent- und Gebrauchsmusterrecht im Jahr 2007*, 110 GRUR 12, 1033-34 (2007) (noting that KSR had been cited by the Federal Court of Justice (BGH) in BGH, GRUR 2008, 145 – Stahlblech and that several statement in KSR on "reasonable expectation of success" and "predictability" correspond with German case law).

[331] As we will see in part II this concerns also national European case law. Of particular interest are a recent series of UK judgments which indicate that the previously very restrictive inventive step threshold in the UK has been slightly lowered through a more cautious interpretation of the "reasonable expectation of success" doctrine.

[332] Krefft, *supra* note 171, at 153-55 (describing how the above described decision in T 500/91 "*Alpha Interferons/Biogen II*" (1992), which concerned an earlier case with underlying facts that were very similar to the situation in *In re Deuel*, demonstrated that the EPO's focus on a reasonable expectation of success and the consideration of secondary indicia could actually guarantee that a hindsight approach was avoided. The EPO found the claimed invention to be non-obvious due to the – at least at that time-high technological unpredictability and the relatively undeveloped prior art. The Board focused *inter alia* on the fact that the specific isolation method had never been tried before with a unique probe and that skilled artisans did not think that this would work. It did so without focusing on structural predictability. It is, however, unlikely that the EPO would subsequently have arrived at the same conclusion as the CAFC in *In re Deuel*. At that time the isolation-method was already generally known and was considered to entail a reasonable expectation of success (a factor which was ignored by the CAFC which focused on the structural predictability of the claimed DNA sequence).

than at the EPO, which does not seem to consider the skilled person to be particularly creative.[333]

At the same time, however, it should also be realized that many of the EPO cases discussed above concerned DNA-related patent applications that were submitted 10-15 years ago. In particular, it should be noted that in the meantime the human genome has been identified as a result of the now completed Human Genome Project (HUGO) and is thus generally known.[334] The early conclusion of HUGO, which together with new sophisticated techniques promoted the publication of a vast number of annotated DNA sequences, as well as the increasing success of similar public projects disclosing a growing number of protein sequences, implies that it has become much more difficult for many DNA-related patent applications to overcome the novelty hurdle.[335]

Moreover, it should be ponted out once more that the research community generally considers the sequencing and mere identification of genes in human and non-human organisms to be a routine process, which normally does not involve any particular difficulties or require innovative activity. Thus, applicants face much greater difficulty when arguing that a particular novel sequence meets the inventive step requirement solely because it has been isolated for the first time.[336] In such cases it might still be possible to argue for an inventive step on the basis of unexpected properties or inventive modifications, as well as on inventive processes and applications for such compounds. Yet, then it will be particularly crucial that the patent application contains *plausible* evidence for such surprising properties or potential applications.

Considering the growing significance of arguments relating to surprising properties in the inventive step assessment, it is worth adding that many of the genes which build up the various genomes existing in nature exhibit a high homology among various organisms, i.e. they have similar sequences. In other words, the annotation of a function for a specific gene, such as a DNA sequence in a mouse, is not necessarily limited to the organism from which it was isolated. Thus a person skilled in the art can be assumed to realize that corresponding genes also exist in other organisms, such as in humans, and that they fulfill similar functions. Yet, in order to meet the inventive step requirement, a DNA-related invention that routinely utilizes the homology of corresponding genes in other organisms in order to isolate and annotate a particular DNA or protein sequence will usually need to demonstrate that the claimed sequence has *truly* surprising properties in relation to the previously known

---

[333] *Cf.* Meier-Beck, *supra* note 330, at 1033-34 (emphasizing that it remains to be seen if the attempt to avoid an overly formal application of the non-obviousness criteria by introduction of the often mockingly called "common-sense-test" would not lead to an erosion of legal certainty. He further states that the focus of German and European case law on the solely decisive "non-obviousness" criteria (or in German: "das allein massgebliche Kriterium des Nicht-Naheliegens", *cf.* BGHZ 168, 142 = GRUR 2006, 842, para 17f.-Demonstrationsschrank), would presumably not allow , to base a obviousness finding on the necessarily speculative assumption , that the invention was merely a product of "normal creativity".). *Cf.* the criticism by D.E.F. Slopek, *Die Behandlung von Trivialpatenten in den USA: US Supreme Court in KSR International Co.v. Teleflex*, 57 GRUR Int 479 (6/2008) (observing that t is questionable if the flexible approach of the KSR decision is a contribution to legal certainly and predictability).

[334] *Cf.* the remarks in SOU 2008:20, Patentskydd för biotekniska uppfinningar (SOU 2008:20), 188, *available at* http://www.regeringen.se/sb/d/10025/a/100513 (last visit 10 May 2009) (including a summary in English).

[335] *See* Minssen, *supra* note 14, at 79-96. However, it should be underlined that the science of human proteomics is not yet as far developed as human genomics. Moreover, there are still several possibilities to base novelty of proteins on the doctrine of selection inventions. The really decisive questions thus often remain for the inventive step assessment.

[336] *Cf.* Karolina Anna Herrlinger, *Die Patentierung von Krankheitsgenen*, Schriftenreihe des Max Planck Instituts zum gewerblichen Rechtsschutz, Band 137, at 130-31 (Heymanns 2005) (in German); Krefft, *supra* note 171, at 155; Schrell, *supra* note 226, at 786; H.U. Dörries, *Patentansprüche auf DNA – Sequenzen: ein Hindernis für die Forschung?*, Mitt. 2001, 15; A. Fuchs, *Patentrecht und Humangenetik*, Mitt 2000, 1, 5; (all in German) (noting that the number of novel sequences is diminishing rapidly).

gene(s).[337] This is, however, rarely the case as it was demonstrated by the case law analysis in the previous chapters.

On the whole, the present situation thus differs considerably from conditions and problems that researchers faced in previous decades. In the 80's and early 90's the development of techniques to identify and isolate specific genes was often still considered to involve innovative activity. Due to the high unpredictability of this at that time relatively new and undeveloped scientific field, the EPO was also more willing to consider the skilled application of these techniques, which sometimes resulted in the identification and isolation of often previously unknown and useful DNA sequences, as a valid reason for the grant of rather broad patents on such sequences. In cases where the mere identification of the sequence was already not considered to be inventive, it was due to the less developed prior art also more likely that the inventive step could be based on secondary evidence, such as unexpected effects. It were in particular the product claims in DNA-related patents granted in this early era, which caused most public arousal, often resulting in challenges that were based on the argument that the scope of protection conferred on these sequences was in light of novel insights about the multifunctionality of DNA unduly broad and that the mere isolation and identification of these sequences should rather be regarded as a discovery.[338]

Returning to the current situation, it is noteworthy that many product patents that were granted for the more interesting DNA sequences in the early days are now expired or will do so very soon. Moreover, in the wake of technological advances, biotechnological science has gradually shifted its focus from the mere sequencing of genomes and isolation of genes to the exploration and exploitation of the specific (often interrelated) functions of particular genes and proteins. The so called science of "functional genomics" and/or "functional proteomics" is a rapidly evolving field of molecular biology that attempts to make use of the vast wealth of data produced by genomic and proteomic projects, such as genome sequencing projects, to describe gene and protein functions and interactions. Unlike genomics and proteomics, functional genomics/proteomics is not so much interested in biological sequences as such. Instead, it focuses on dynamic aspects such as gene transcription, translation, and protein-protein interactions, as opposed to the static aspects of the genomic and proteomic information contained in DNA and protein sequences or structures.[339] This change of focus contributes significantly to a development, wherein innovative efforts are increasingly directed to the specific, often interrelated functions of genes and proteins and not to their mere discovery. There is reason to assume that this will result in a better public acceptance and understanding of what present gene technology is really all about: It is an attempt to technically utilize the processes in which genes and proteins are involved. The growing knowledge about these functions further implies that the scientific and technical state of the

---

[337] *See also* SOU 2008:20, *supra* note 334, at 190 (adding that many recent inventive step related EPO judgments deal with such situations).

[338] *Id.* at 188-89. This debate crystallized in both Europe and the US in the various legal challenges to (and limitations/amendments of) Myriad Genetics BRCA – gene patents. As for the latest developments at the EPO *cf.* note Siva, *Myriad wins BRCA1 row*, Nature Biotechnology 27, 8 (2009). For more information about the recent US challenge (May 2009), *see* Association for Molecular Pathology et. al. v. United States Patent and Trademark Office, et.al., Plaintiff's Complaint, Civil Action No. 09-4515-RWS (2009), *available at* http://www.aclu.org/images/asset_upload_file 939_39568.pdf_(last visited September 3, 2009). See also Turna Ray, *Myriad's BRCA Patents Not Only Illegal, but Also Unconstitutional*, ACLU Lawsuit Alleges, *available at* http://www.genomeweb.com/dxpgx/myriads-brca-patents-not-only-illegal-also-unconstitutional-aclu-lawsuit-alleges (last visit: 10 August 2009).

[339] For further explanation of (functional) proteomics and genomics and an overview of recent techniques applied, *see* Philip Grubb , Patents for Chemicals, *Pharmaceuticals and Biotechnology*, 265 (Oxford University, (4th ed. 2004); *see also* part II of this paper.

art has advanced considerably, and that while more functions are being disclosed, they generally also become more foreseeable and controllable.[340]

The increasing predictability and the expansion of the common general knowledge will presumably lead to two divergent effects in the context of the inventive step assessment. *On the one hand*, an applicant may more easily satisfy the new "plausibility-test" and provide credible evidence with a high probative value for a claimed technical effect, for example, by referring to educated "in silicio" guesses on DNA or protein functions with the help of powerful bio-informatics tools and methods or by basing their technical conclusions on DNA sequence homologies to better known genes.[341] *On the other hand*, the very same technical advances will probably cause the applicant greater difficulty in showing that the technical contribution claimed, or the plausible solution to the identified problem, would not have been obvious or predictable for a person skilled in the art and thus was inventive. As it has been indicated above, applicants will in particular face an increasingly tough challenge in demonstrating that there was no "reasonable expectation of success" involved in the isolation and annotation of a gene, or even a protein. At least thus far applicants could then often rely on secondary indicia, such as plausibly disclosed and truly unexpected effects or functions. Yet, due to the rapid expansion of the state of the art and common general knowledge, it can be assumed that in the future it will become ever more difficult to demonstrate that specific properties and functions for biochemical compounds, including partcularly DNA and protein sequences with known homologues in other organisms, were indeed truly surprising for a person skilled in the art.[342]

Another contributing factor to the changes in the European patent landscape is the fact that the EPO, as well as many national patent offices, have in the recent years adopted a more sophisticated examination and restrictive interpretation of the inventive step criteria. They also require more reliable data that plausibly supports the patent claims. This finding is supported by the case law previously discussed, and has also been recognized in several publications by national and international research projects, as well as in reports from government-appointed committees.[343] Moreover, the EPO itself has recently published

---

[340] However, this should not conceal that many questions still remain, since genes and proteins interact and can fulfill multiple function at technically different locations. Moreover, during recent years scientists have understood that biological fate is not regulated solely by straightforward DNA sequence - protein interactions, but that super ordinate regulatory mechanisms exist and contribute to determine the function and expression of genes. Research has shown that these mechanisms - broadly defined as Epigenetics - are multifaceted and complex. At the same time, rapidly developing recent technologies have made it possible (and increasingly cheaper and faster) to profile the key molecular players of histone modification and DNA methylation from regulation in normal embryogenesis through changes in epigenetic state that plays a central role in disease. Understanding this regulation can lead to biomarker identification for monitoring drug effects, toxicity and effective dose for therapeutic intervention as well as diagnostic and prognostic tools for disease. *See also* L.M. Butcher & S. Beck, *Future Impact of integrated high-throughput methylome analyses on human health and disease*, 35 JOURNAL OF GENETICS AND GENOMICS, 391 - 401 (2008) (for a more detailed discussion, see part II).

[341] In that context it should once again be realized that raising the level of skill of the skilled person would have an effect not just on inventive step, but also on sufficiency of disclosure and clarity, and in these cases, the consequence would be a "lowering of the bar" for these requirements, *cf.* G. Ashley, *supra* notes. 114 & 141.

[342] It should, however, be understood that, despite the recent advances (see part II), the science of functional proteomics is not quite as far developed as the science of functional genomics. Due to the complexity of protein-expression, protein- structures, their inter-relations and thus potential functions, "surprising effects" might still provide common arguments for non-obviousness.

[343] *See* the PATGEN Project-report, *The Patenting of Human DNA: Global Trends in Public and Private Sector Activity* (November 2006), *available at* http://www.sussex.ac.uk/spru/documents/patgen_finalreport.pdf (noting that, "[d]ebates on the patenting of human DNA need to reflect the disparities between patenting activity in the US and elsewhere. Moreover, with the number of DNA-related patent applications in decline, more stringent examination procedures, and the likely restriction of the scope of granted patents by case law, suggest that the

several policy announcements and has adopted specific measures, which clearly indicate that the EPO is conducting severe efforts to "raise the bar" for the basic patentability requirements and to improve the effectiveness of the granting procedure.[344] These documents often emphasize that one major goal is to heighten the quality standard of the patents granted by the EPO. This entails the plan to conduct a more stringent and more critical examination of patent applications. The goal is to grant patents only to technical inventions that present a sufficiently significant new contribution to the state of the art or in other words, a true progress in the expansion of knowledge. It is *inter alia* hoped that this will help to prevent the creation of so-called patentthickets with a dense web of overlapping, often trivial, patents rights surrounding one field of technology with interesting applications. Moreover, the strict application of the patentability standards is also considered to be an important factor in controlling the number of patent applications being filed.[345] These developments and EPO policy statements have now also been expressly recognized and welcomed in the much debated final "Pharmaceutical Sector Inquiry" report, which had been adopted by the European Commission on July 9th, 2009.[346]

In summary, it can be concluded that the EPO conducts the inventive step assessment of biotechnological inventions with an appropriately restrictive but nevertheless well-balanced attitude. This attitude, which is also reflected in the application of the other basic patentability requirements, takes a particular effect on the number and type of patent claims that are granted for DNA and protein-related technology.[347] This effect is enhanced due to the fact that the recent legal developments are accompanied by rapid technological developments

---

negative impact of DNA patenting may turn out to be more limited than some had feared. Finally, referring to the increase in the thresholds for patentability perceived by interviewees it was suggested that patent offices are focused on providing due rewards."); *see also* Andrew Gowers, *Review of Intellectual Property* (Nov. 2006), *available at* http://ec.europa.eu/internal_market/copyright/docs/links/gowers_report_en.pdf, and the UKIPO report, Public consultation on level of the inventive step required for obtaining patents (2007), *available at* http://www.ipo.gov.uk/response-inventive.pdf (noting *inter alia* a well balanced inventive step assessment at the UKIPO with a sufficiently high inventive step threshold. It is further found that UK courts tended to be even more restrictive in their inventive step assessment. Yet, as it will be discussed in part II that seems to have changed); *cf.* SOU, *supra* note 334, at 188-90 (last visits 20 September 2009).

[344] *See supra* note 324; *see* also the speech by the EPO president Alison Brimelow, *Patent Office Insights on Trilateral Process: Past Successes and Future Challenges* (2007), *available at* http://www.trilateral.net/events/meetings/2007/brimelow.pdf (last visit 20 July 2009) (highlighting the need of multinational office corporation to enhance patent quality and to control the over-all increase of patent filings.).

[345] For further statistical info see the EPO publication at: http://www.epo.org/topics/news/2009/20090317.html (last visit 20 July) (pointing out that the over-all number of European patent applications has continued to increase in 2008, albeit at a much lower level, and that the grant rate for European patents dropped for the first time to less than 50% (49.5%; 2007: 51%). Moreover, Alison Brimelow is quoted, emphasizing *inter alia* the need for an effective quality policy in patents and adding: "Some efforts in this respect are now beginning to bear fruit: The practice we introduced in 2004 of informing applicants early in the process of their prospects of obtaining a patent visibly encourages companies in many cases to abandon their applications. Subsequently, the strict application of patentability criteria by our patent examiners has led to more refusals to grant a patent." Interestingly, it also stated that while the filing activity in medical technologies has increased by 11.6 %, the filings in biotechnology and genetic engineering have decreased by 0.9 %.).

[346] *See* Final Report by the EC Commission on its competition inquiry into the pharma sector, *available at* http://ec.europa.eu/comm/competition/sectors/pharmaceuticals/inquiry/index.html (last visit 8 August 2009) (urging MS to enhance stronger competition in the pharma- sector by strengthening the generic industry through a variety of measures. Concerning patent issues it is *inter alia* noted that there is an urgent need for the establishment of a Community patent and a unified specialized patent litigation system in Europe. Moreover, it is pointed out that the recent initiatives of the EPO to ensure a high quality standard of patents granted and to accelerate procedures are welcomed. In particular, the Commission highlights the significance of the inventive step requirement and the measures taken in March 2009 to limit the possibilities and time periods during which voluntary divisional patent applications can be filed (so called "raising the bar exercise")). Yet, it should be understood that many findings in the report had been heavily criticized during the public consultation procedure.

[347] *See supra* note 345 & Hopkins et al, *supra* note 4, at 186-87.

in biotechnology. As a result, the conditions for potential situations in which DNA-related patent may be granted have changed considerably. Rapid scientific advances coupled with increasing significance of functional genomics and proteomics implies that the identification and development of particular innovative therapeutic applications with DNA and protein-related mechanisms have become the central issue in assessing whether a claimed invention meets the inventive step criteria. As for the near future, it can further be assumed that in a growing number of cases relating to so-called "second-" and "third generation" DNA technology, the naturally occurring DNA or even protein sequence with which specific and perhaps patentable applications have been developed, will more often *not* be patentable as such. This is because it will become more likely that the sequence was either already known, too easy to identify/modify or too predictable with regard to its properties. While much will presumably still depend on how the standard for selection inventions and secondary indicia, such as the threshold for what will be considered to be truly surprising properties, develops in the light of technological advances, there is good reason to expect that the innovative activity of patent seeking scientists will increasingly result in narrower patent claims. Such claims will most likely focus on novel and truly inventive therapeutic methods, personalized drugs or further uses of, perhaps modified, DNA or protein- related inventions.[348] In that way, the basis for the grant of patents will hopefully become more apparent and understandable. In turn, this might facilitate the much needed public acceptance and trust in the patent system. Due to the more apparent role of inventive human intervention, it can particularly be presumed that there will be fewer situations in the future, where the dividing line between an invention and a mere discovery is rather blurred and thus difficult to justify or explain to the concerned public.[349] Another much welcomed additional effect of such a development would also be that such EPO patents unmistakably satisfy the requirements stipulated in article 5 (3) of the EC Biotech Directive,[350] which explicitly requires that the industrial application of a sequence or partial sequence of a gene is disclosed in the patent application.[351]

---

[348] Hopkins et al, *supra* note 4, at 185, 187 (noting that it has both in the US and Europe become more difficult to patent research tools including DNA fragments such as ESTs. It is further added:"On future strategies, some interviewees indicated that they will now focus on new uses for known rather than novel sequences, with applications now likely to require greater preparation and more biological data to support narrower claims. Diagnostic/prognostic tests based on gene expression profiling or single nucleotide polymorphisms (SNPs), and therapeutics based on RNA interference were identified as new areas for patenting, although doubts were expressed by a minority over the likelihood of such inventions obtaining satisfactory patent protection...." Thus it can be argued that the focus seems to shift from upstream research tools to downstream applications.).

[349] This is in particular so whenever specific functions have been designed through inventive chemical modifications or where inventive applications have been developed through human intervention. It is then difficult to speak of a mere "product of nature". Yet, many applications will necessarily have to involve natural "processes" or "phenomenons", which is why the patentability of such inventions will presumably remain debated in both Europe and the US. *See* Shun-liang Hsu, *The Paradox Facing DNA Patenting in Europe*, 3 JOURNAL OF INTERNATIONAL BIOTECHNOLOGY LAW 2, 72–83 (2006). For a discussion of recent US "patent eligibility" developments, *see* Christopher Holman, *Bilski: Assessing the Impact of a Newly Invigorated Patent Eligibility Doctrine on the Pharmaceutical Industry and the Future of Personalized Medicine* (2009), *available at* http://ssrn.com/abstract=1424493 (last visit 20 July 2009) (discussing (potential) impacts of new case law developments, such as *In re Bilski* (soon to be decided by the Supreme Court), on the scope of protection that will be conferred on biopharmaceutical patents); *see also* the most recent CAFC decision in *Prometheus Labs, Inc. v. Mayo Collaborative Servs.*, 581 F.3d 1336 (Fed.Cir. 2009).

[350] *Cf. supra* note, 27 & 28. It should, once again, be noted that the EPO is not formally bound by the Directive.

[351] *See* the recitals 8 (2), 23, 24 and 25 of the Biotech Directive. Another question is, of course, if such an industrial application should necessarily have to be included in patent claims on DNA-related technology. In that regard, see also recitals 8 (1), 12, 17, 22, 28 and 46 of the Biotech Directive, as well as Art. 27 TRIPS. Yet, this question will become less significant, if future patents on DNA related technology would - merely by strictly interpreting the classical patentability requirements - predominantly be limited to methods and applications for such sequences. In that way, the standard that will be set for inventive step and the other patentability requirements will have a great impact on the "anticommons" and scope of protection discussion in

While these effects certainly represent the positive outcomes of a heightened inventive step threshold, there might, however, also be serious drawbacks involved. The envisaged problems pertain to a scenario where the pharmaceutical industry will discard a growing number of old or obvious, and thus unpatentable, compounds as well as potentially significant but predictable therapeutic applications from the expensive R&D process, which otherwise might have resulted in highly beneficial drugs. More precisely the crucial question will most likely be: Who will be willing to, or should, conduct the sophisticated research and the risky and expensive clinical trials needed for market approval of biopharmaceuticals if sufficient patent protection is no longer available to guarantee a return of investment? After an analysis of recent developments in the UK, where courts seem to have recognized the growing problems, as well as a short comparative discussion of the U.S. situation, this central question and potential solution proposals will be discussed in Part II.

Europe. As a matter of fact this fierce debate has resulted in divergent national implementing legislations that either have introduced categorical purpose bound product protections for DNA-related inventions, or have still left open the possibility of receiving full product patents (like it is the case at the EPO and the USPTO). For more details *see* Timo Minssen, *Es Bleibet Dabei: Eine Schwedische Stellungnahme zur Europäischen Debatte über den Absoluten Erzeugnisschutz bei der DNA Patentierung*, KliFoR 3 & 4, 93-120 (2008) (in German), *available at* http://www.lu.se/o.o.i.s?id=12588&search=link&author=jur-tmi (last visit 10 January 2010) (arguing that as long as a stricter application of the patentability requirements guarantees that full product protection is only granted for sequences in exceptional and well founded cases, there is at present no imminent need for the introduction of a categorical purpose limitation. Yet, the situation has to be monitored and sufficient post-grant mechanisms must be made available in order to properly address extreme cases. If the number of product patents with a scope of protection that does not correspond to the inventors actual contribution to the state of the art would still grow, it might be reasonable in cases were the inventive step is merely based on the identification of a surprising property to restrict the protection to that specific property.); *see also* Joseph Straus, *Product patents on human DNA sequences: where do we stand in Europe*, 326 COMPTES RENDUS BIOLOGIES 10-11, 1111-14 (2003).