CHAPTER 7

NON-OBVIOUSNESS

Non-obviousness or Inventive step is one of the most important but uncertain patentability filters. The non-obviousness requirement has been called "the ultimate condition of patentability[499]." To be patentable, an invention has to be non-obvious in the light of the prior art at the time of invention. Non-obviousness is determined from the point of view of a person with ordinary skill in the art. While novelty is decided in the light of a single prior art reference, non-obviousness is decided in the light of combined prior art references. Issues surrounding motivation or suggestion to combine, ascertainment of level of ordinary skill, value of secondary indications, etc, in relation to biotechnology and specifically genes or gene based inventions make the non-obviousness filter very complex. This filter plays a very important role in defining the size of patent domain by ensuring that only inventions having an inventive element enter into it.

USA

Non-obviousness in United States is governed by section 103 of the United States Code[500]. As per the section, an invention satisfies this requirement if it is not obvious inn the light of prior art to a person with ordinary skill in the art[501]. An analysis of non-obviousness is based on several factual inquiries such as,

(1) The scope and content of the prior art;

(2) The differences between the prior art and the claims at issue;

(3) The level of ordinary skill in the art at the time the invention was made; and

(4) Objective evidence of non-obviousness, if any[502].

The requirement checks whether a person of ordinary skill in the art who knew the entire prior art would have had a reasonable expectation that the invention

[499] NONOBVIOUSNESS--THE ULTIMATE CONDITION OF PATENTABILITY (John Witherspoon ed., 1980).
[500] 35 USC Sec. 103.
[501] Id.
[502] Graham v. John Deere Co., 383 U.S. 1, 17-18, 86 S.Ct. 684, 693-94 (1966).

would work[503]. To make an invention obvious, there must be a suggestion in the prior art to combine the prior art elements in the way in which they are combined in the claimed invention[504]. An invention will not be obvious if it was merely obvious to try in the light of prior art[505]. 'Obvious to try' is not considered by the patent office and the courts to be obviousness. It exists when it is necessary 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[506]. 'Obvious to try' also exists in a situation requiring exploration of 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[507]. Determination of obvious to try or obviousness has been very controversial when it comes to genes or gene based inventions.

The Federal Circuit has been attempting to resolve complications surrounding motivation to combine prior art, level of ordinary skill in the art, reasonableness of success and so on through its decisions.

Hybritech v. Monoclonal[508]

The claims in the patent at issue in this case relate to a variety of sandwich assays using monoclonal antibodies[509]. The district court held the claims of the '110 patent invalid for obviousness from the Oi/Herzenberg work in view of a February 1979 article by M.E. Frankel and W. Gerhard (Frankel article) which

[503] Loctite Corp. v. Ultraseal, Ltd., 781 F.2d 861, (Fed. Cir. 1985).
[504] Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co., 730 F.2d 1452, 1462, (Fed. Cir. 1984).
[505] Merck & Co. v. Biocraft Labs., 874 F.2d 804, 807, (Fed. Cir. 1989).
[506] In re Geiger, 815 F.2d at 688, 2 USPQ2d at 1278.
[507] In re Dow Chemical Co., 837 F.2d 469, 473, (Fed.Cir.1988).
[508] Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367 (C.A.Fed. (Cal.),1986).
[509] Id.

discloses high-affinity monoclonal antibodies, and in view of numerous other references[510].

The court started its reasoning by stating that non-obviousness would be determined by checking whether the claimed invention would have been obvious at the time the invention was made and objective evidence such as commercial success, failure of others, long-felt need, and unexpected results would be considered before a conclusion on non-obviousness is reached[511]. In its determination, the court first considered eight articles predicting Widespread Use of Monoclonal Antibodies[512]. The eight articles predicted that the breakthrough in production of monoclonal antibodies by Kohler and Milstein would lead to widespread use of monoclonal antibodies in immunoassays[513]. The court stated that four of those articles are not prior art as they lack priority over the claimed invention in question. Though the other four predict immunoassays, the court said that none of them disclose sandwich assays and pointed out that the four articles are invitations to try monoclonal antibodies in immunoassays but do not suggest how that end might be accomplished[514]. Therefore, the court held the claimed invention to be not obvious in the light of all eight articles.

The court then considered Kohler and Milstein work, which involved a method developed for producing monoclonal antibodies in vitro and held that it does not make the claimed invention obvious because it does not suggest using monoclonal antibodies in a sandwich assay in accordance with the invention claimed in the patent[515]. Further, the court stated that the Cuello reference discloses monoclonal antibodies but not in a sandwich assay[516]. Though the Jeong patent discloses the use of polyclonal antibodies in a simultaneous

[510] Id. at 1379.
[511] Id. at 1380.
[512] Id.
[513] Id.
[514] Id.
[515] Id.
[516] Id.

sandwich assay, the court was of the view that it had no suggestion that monoclonal antibodies can be so used[517].

The court then analyzed the Oi/Herzenberg work, which involved mapping epitopes on a known quantity of antigen[518]. It concluded that the Oi/Herzenberg work was qualitatively different than the claimed invention because the former is directed to mapping epitopes on a known quantity of antigen and the latter to determining the "presence or concentration of an antigenic substance in a sample of fluid[519]. Furthermore, the court stated that it is perfectly clear that the Oi/Heizenberg work in no way suggests using monoclonal antibodies of the affinity claimed in the claimed invention[520]. Because of these differences between the Oi/Herzenberg work and the claimed invention that the fact that an antigen was sandwiched between two monoclonal antibodies in the course of Oi's and Herzenberg's work, the court held that it is not sufficient basis to conclude that the claimed invention would have been obvious at the time it was made to a person of ordinary skill in the art[521].

The court then considered a combination of Oi/Heizenberg work and Frankel article, which teaches a method for rapid determination of affinity constants for monoclonal antibodies, some of which clearly have affinities of the order defined by the claimed invention[522]. It stated that the mere existence of prior art disclosing how to measure the affinity of high affinity monoclonal antibodies would be insufficient to support a holding of obviousness[523]. As Frankel article fails to suggest using such antibodies in a sandwich assay, it does not compensate for the substantial difference between the Oi/Herzenberg

[517] Id.
[518] Id. at 1381.
[519] Id.
[520] Id.
[521] Id.
[522] Id.
[523] Id.

work and the claimed invention, and therefore those references in combination cannot support a holding of obviousness[524].

The court then considered objective Evidence of non-obviousness. The sales of Hybritech's diagnostic kits increased seven million dollars in just over one year, from $6.9 million in 1983 to an estimated $14.5 million in 1984 and Hybritech's kits occupied twenty five percent of the market, which is an indication of tremendous commercial success[525]. The court stated that the tremendous and prolonged commercial success was due to the non-obviousness of the claimed invention[526].

In the light of the analysis, the court held the claimed invention to be non-obvious because the large number of references, as a whole, relied upon by the district court to show obviousness, skirt all around but do not as a whole suggest the claimed invention.

The case elucidates that existence of discrete prior art with missing links would not make an invention obvious. It further reiterates that obvious to try would not make an invention obvious. The case illustrates the importance of prior art references in making an obviousness determination.

In re O'Farrell[527]

In re O'Farrell relates to a patent application concerning a method and Hybrid Vector for Regulating Translation of Heterologous DNA in Bacteria[528]. The inventors reduced their invention to practice some time in 1976 and reported their results in a paper that was published in 1978 ('Polisky reference')[529].

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[524] Id.
[525] Id. at 1382.
[526] Id.
[527] In re O'Farrell, 853 F.2d 894 (C.A.Fed.,1988).
[528] Id. at 896.
[529] Id.

During 1977 they communicated their results to another group of researchers who used the read through translation approach to achieve the first synthesis of a human protein in bacteria[530]. The inventors then filed an application to patent their invention on August 9, 1978, of which the application on appeal is a division[531].

The court stated that the claimed invention would have been obvious in light of the Polisky reference alone or in combination with Bahl reference within the meaning of Section 103 because Polisky contained detailed enabling methodology for practicing the claimed invention, a suggestion to modify the prior art to practice the claimed invention, and evidence suggesting that it would be successful[532]. Though the inventors argued that after the publication of Polisky, successful synthesis of protein was still uncertain the court was of the view that since nonsense RNA produced nonsense polypeptides, if meaningful RNA was inserted instead of ribosomal RNA, useful protein would be the result, thesynthesis of the protein was not uncertain[533]. It further stated that the relative shortness of the added chains is also not a source of uncertainty, since one skilled in the art would have known that a random sequence of nucleotides would produce a stop codon before the chain got too long[534].

The court pointed out that obviousness does not require absolute predictability of success but only reasonable predictability of success and that for many inventions that seem quite obvious, there is no absolute predictability of success until the invention is reduced to practice[535]. It then went on to state that the Polisky reference, when combined with the Bahl reference provided such a reasonable expectation of success. As inventors provided virtually all of

[530] Id. at 897.
[531] Id.
[532] Id. at 902.
[533] Id.
[534] Id.
[535] Id. at 903.

their method to the public without applying for a patent within a year, the court concluded that they foreclosed themselves from obtaining a patent on a method that would have been obvious from their publication to those of ordinary skill in the art, with or without the disclosures of other prior art[536].

The case elucidates that obviousness requires reasonable predictability of success from the prior art in order to bring it outside the scope of 'Obvious to try' and make it obvious. The maturity of the field is considered for such a determination through the eyes of a person with ordinary skill. The inventor's own publication can make his invention obvious if reasonable steps are not taken.

In re Vaeck[537]

This case relates to a patent including a chimeric gene comprising a gene derived from a bacterium of the Bacillus genus whose product is an insecticidal protein, united wit a DNA promoter effective for expressing the Bacillus gene in a host cyanobacterium, so as to produce the desired insecticidal protein[538]. The Patent Examiner and the Board rejected the claimed invention as obvious under section 103 of the United States Code based upon certain prior art references.

The court started its analysis by stating that rejection of a patent based on combined prior art references requires consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable

[536] Id. at 904.
[537] In re Vaeck, 947 F.2d 488 (C.A.Fed.,1991).
[538] Id.

expectation of success[539]. As per the court, both the suggestion and the reasonable expectation of success must be founded in the prior art, and not in the applicant's disclosure[540].

The court pointed out that there is no suggestion in Dzelzkalns, which is the primary reference cited against all claims, of substituting in the disclosed plasmid a structural gene encoding Bacillus insecticidal proteins for the CAT gene utilized for selection purposes because the expression of antibiotic resistance-conferring genes in cyanobacteria, without more, does not render obvious the expression of unrelated genes in cyanobacteria for unrelated purposes[541]. It brushed aside the Patent Office's arguments that the substitution of insecticidal Bacillus genes for CAT marker genes in cyanobacteria is suggested by the secondary references Sekar I, Sekar II, and Ganesan, which collectively disclose expression of genes encoding Bacillus insecticidal proteins in two species of host Bacillus bacteria (B. megaterium and B. subtilis) as well as in the bacterium E. coli. It stated that though the references disclose expression of Bacillus genes encoding insecticidal proteins in certain transformed bacterial hosts, these references do not disclose or suggest expression of such genes in transformed cyanobacterial hosts[542].

Though the patent office emphasized similarity between bacteria and cyanobacteria, by stating that both are procaryotic organisms, and argued that this fact would suggest to those of ordinary skill the use of cyanobacteria as hosts for expression of the claimed chimeric genes, the court stated that even if both are classified as procaryotes, that fact alone would not be sufficient to motivate the art worker[543]. The court went on to state that cyanobacteria and bacteria are not identical as they are classified as two separate divisions of the

[539] Id. at 493.
[540] Id.
[541] Id.
[542] Id.
[543] Id.

kingdom Procaryotae[544]. Evidence of recent uncertainty regarding the biology of cyanobacteria as per the court tends to rebut, rather than support, the patent office's position that one would consider the cyanobacteria effectively interchangeable with bacteria as hosts for expression of the claimed gene. Furthermore, the court stated that Dzelzkalns, Sekar I, Sekar II, Ganesan references and additional references do not suggest that cyanobacteria could serve as hosts for expression of genes encoding Bacillus insecticidal proteins[545]. It pointed out that these additional references suggest as much about differences between cyanobacteria and bacteria as they do about similarities.

Though the relevant prior art does indicate that cyanobacteria are attractive hosts for expression of both native and heterologous genes involved in photosynthesis the court pointed out that prior art references do not suggest that cyanobacteria would be equally attractive hosts for expression of unrelated heterologous genes, such as the claimed genes encoding Bacillus insecticidal proteins[546]. In contrast with the situation in O'Farrell, the court stated that the prior art in this case offers no suggestion, explicit or implicit, of the substitution of bacteria with cyanobacteria and there was no reasonable expectation of success, which is the difference between the claimed invention and the prior art[547].

In the light of the reasoning, the court held that the claimed invention is non-obvious because the prior art does not disclose or suggest the expression in cyanobacteria of a chimeric gene encoding an insecticidally active protein, or convey to those of ordinary skill a reasonable expectation of success in doing so.

[544] Id. at 494.
[545] Id.
[546] Id.
[547] Id. at 495.

The case elucidates that existence of a prior art reference indicating expression of genes in one species does not make the expression of the genes in other species obvious.

Amgen v. Chugai[548]

Amgen relates to a patent for DNA sequences encoding Erythropoietin (EPO)[549]. In a patent infringement suit filed by the appellants, the defendants claimed that the patent is obvious in the light of prior art and therefore invalid[550]. The Defendants argued that, as of September 1983, one of ordinary skill in the art would have had a reasonable expectation of success in screening a gDNA library by Lin's method in order to obtain EPO[551]. As experts opined that it would have been difficult to isolate the EPO gene in the year 1983 based on the prior art and that the chances of isolating were only fifty percent because the probes being used were fully degenerate, the court rejected the defendants' argument and stated that the claimed invention was not obvious[552]. The court also rejected the obviousness argument of the defendants based on homology with monkey gene by stating that though it might have been feasible, perhaps obvious to try, to successfully probe a human gDNA library with a monkey cDNA probe, it does not indicate that the gene could have been identified and isolated with a reasonable likelihood of success because neither the DNA nucleotide sequence of the human EPO gene nor its exact degree of homology with the monkey EPO gene was known at the time[553]. The court went on to say that while the idea of using the monkey gene to probe for a homologous human gene may have been obvious to try, the realization of that idea would not have been obvious[554]. In the light of its analysis, the court held the claimed invention to be not obvious and reiterated that hindsight is not a justifiable

[548] Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd., 927 F.2d 1200 (C.A.Fed. (Mass.),1991).
[549] Id.
[550] Id.
[551] Id. at 1208.
[552] Id.
[553] Id.
[554] Id.

basis on which to find that ultimate achievement of a long sought and difficult scientific goal was obvious[555].

The case elucidates that homology with the gene sequence of other species and existence of general methods of isolating genes would not make an isolated gene sequence obvious.

In re Bell[556]

The claims of the application at issue in this case are directed to nucleic acid molecules (DNA and RNA) containing human sequences, which code for human insulin-like growth factors I and II(IGF), single chain serum proteins that play a role in the mediation of somatic cell growth following the administration of growth hormones[557]. The relevant prior art consisted of two publications by Rinderknecht disclosing amino acid sequences for IGF-I and -II and U.S. Patent 4,394,443 to Weissman et al., entitled Method for Cloning Genes[558]. Weissman described a general method for isolating a gene for which at least a short amino acid sequence of the encoded protein is known. The Weissman patent specifically described the isolation of a gene, which codes for human histocompatibility antigen, a protein unrelated to IGF. The examiner rejected the claims as obvious over the combined teachings of Rinderknecht and Weissman[559].

The court started its analysis by stating that a prima facie case of obviousness is established when the teachings from the prior art itself would appear to have suggested the claimed subject matter to a person of ordinary skill in the art[560]. Though it may be true that, knowing the structure of the protein, one can use

[555] Id.
[556] In re Bell, 991 F.2d 781 (C.A.Fed.,1993).
[557] Id. at 782.
[558] Id.
[559] Id.
[560] Id. at 783.

the genetic code to hypothesize possible structures for the corresponding gene and that one thus has the potential for obtaining that gene, the court pointed out that considering the degeneracy of the genetic code, there are a vast number of nucleotide sequences that might code for a specific protein[561]. As the Rinderknecht amino acid sequences could be coded for by more than 1036 different nucleotide sequences, only a few of which are the human sequences that the inventor claims and given the nearly infinite number of possibilities suggested by the prior art, and the failure of the cited prior art to suggest which of those possibilities is the human sequence, the court stated that the claimed sequences would not have been obvious[562]. As the inventor claims only the human nucleic acid sequences coding for IGF, absent anything in the cited prior art suggesting which of the 1036 possible sequences suggested by Rinderknecht corresponds to the IGF gene, the court further stated that the prior art does not suggest the claimed invention[563].

The court then said that combining Rinderknecht with Weissman does not fill the gap. It explained by stating that obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination[564]. The court was of the view that Weissman discloses a general method for isolating genes, which appears to teach away from the claimed invention by emphasizing the importance of unique codons for the amino acids[565]. As the inventor used a probe having 23 nucleotides based on a sequence of eight amino acids, none of which were unique, the court stated that Weissman tends to teach away from the claimed sequences since Rinderknecht shows that IGF-I has only a single amino acid with a unique codon and IGF-II has none[566]. The court further stated that Weissman does not suggest that its teachings should be combined with

[561] Id. at 784.
[562] Id.
[563] Id.
[564] Id.
[565] Id.
[566] Id.

those of Rinderknecht, since it nowhere suggests how to apply its teachings to amino acid sequences without unique codons[567]. It went on to say that the requisite teaching or suggestion to combine the teachings of the cited prior art references was absent[568]. In the light of its analysis, the court concluded that the combination of prior art references does not render the claimed invention obvious,

The case elucidates that combination of a prior art reference disclosing a general method of isolating DNA sequences coding for proteins without reference to a specific protein combined with a partial sequence would not make the complete sequence obvious.

In re Deuel[569]

In In re Deuel, the claimed invention relates to isolated and purified DNA and cDNA molecules encoding heparin-binding growth factors ("HBGFs")[570]. The inventor, Deuel, isolated and purified HBGF from bovine uterine tissue, found that it exhibited mitogenic activity, and determined the first 25 amino acids of the protein's N-terminal sequence[571]. Deuel then isolated a cDNA molecule encoding bovine uterine HBGF by screening a bovine uterine cDNA library with an oligonucleotide probe designed using the experimentally determined N-terminal sequence of the HBGF[572]. He purified and sequenced the cDNA molecule, which was found to consist of a sequence of 1196 nucleotide base pairs. From the cDNA's nucleotide sequence, Deuel then predicted the complete amino acid sequence of bovine uterine HBGF disclosed in Deuel's application[573].

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[567] Id. at 785.
[568] Id.
[569] In re Deuel, 51 F.3d 1552 (C.A.Fed.,1995).
[570] Id. at 1554.
[571] Id. at 1555.
[572] Id.
[573] Id.

Deuel also isolated a cDNA molecule encoding human placental HBGF by screening a human placental cDNA library using the isolated bovine uterine cDNA clone as a probe[574]. He purified and sequenced the human placental cDNA clone, which was found to consist of a sequence of 961 nucleotide base pairs[575]. From the nucleotide sequence of the cDNA molecule encoding human placental HBGF, Deuel predicted the complete amino acid sequence of human placental HBGF disclosed in Deuel's application[576]. The predicted human placental and bovine uterine HBGFs each have 168 amino acids and calculated molecular weights of 18.9 kD[577]. Of the 168 amino acids present in the two HBGFs discovered by Deuel, 163 are identical[578]. Deuel's application does not describe the chemical structure of, or state how to isolate and purify, any DNA or cDNA molecule except the disclosed human placental and bovine uterine cDNAs[579].

The patent office and the board rejected Deuel's patent application by stating that his invention is obvious in the light of Maniatis and Bohlen references[580]. They asserted that, given Bohlen's disclosure of a heparin-binding protein and its N-terminal sequence and Maniatis's gene cloning method, it would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to clone a gene for HBGF. The Federal Circuit rejected the conclusion of the patent office.

The court started its analysis by stating that the teachings of the prior art should suggest the claimed compounds to a person of ordinary skill in the art[581]. Though Maniatis suggests an allegedly obvious process for trying to isolate cDNA molecules, the court pointed out that it would not fill the gap of

[574] Id.
[575] Id.
[576] Id.
[577] Id.
[578] Id.
[579] Id.
[580] Id.
[581] Id. at 1558.

the claimed invention[582]. Further, while the general idea of the claimed molecules, their function, and their general chemical nature may have been obvious from Bohlen's teachings, and the knowledge that some gene existed may have been clear, the court stated that the precise cDNA molecules are not obvious over the Bohlen reference because Bohlen teaches proteins, not the claimed or closely related cDNA molecules[583]. Moreover, the court stated that the redundancy of the genetic code precluded contemplation of or focus on the specific cDNA molecules in the claimed invention[584]. Thus, the court concluded that one could not have conceived the subject matter of the invention based on the teachings in the prior art references because, until the claimed molecules were actually isolated and purified, it would have been highly unlikely for one of ordinary skill in the art to contemplate what was ultimately obtained[585]. What cannot be contemplated or conceived cannot be obvious.

Furthermore, the court pointed out that the patent office's theory that one might have been motivated to try to do what Deuel in fact accomplished amounts to speculation and an impermissible hindsight reconstruction of the claimed invention[586]. It went on to say that a general motivation to search for some gene that exists does not necessarily make obvious a specifically defined gene that is subsequently obtained as a result of that search[587]. The court reasoned that the genetic code relationship between proteins and nucleic acids does not overcome the deficiencies of the cited references because a prior art disclosure of the amino acid sequence of a protein does not necessarily render particular DNA molecules encoding the protein obvious as the redundancy of the genetic code permits one to hypothesize an enormous number of DNA sequences coding for the protein[588]. It went on to say that no particular one of the DNAs in the claimed invention can be obvious unless there is something in

[582] Id.
[583] Id.
[584] Id.
[585] Id.
[586] Id.
[587] Id.
[588] Id.

the prior art to lead to the particular DNA and indicate that it should be prepared[589]. Thus, the court concluded that Bohlen's disclosure of the N-terminal portion of a protein, which the patent office urges is the same as HBGF, would not have suggested the particular cDNA molecules[590].

Though the existence of general cloning techniques, coupled with knowledge of a protein's structure, might have provided motivation to prepare a cDNA or made it obvious to prepare a cDNA, the court pointed out that it does not necessarily make obvious a particular claimed cDNA[591]. As per the court "Obvious to try" has long been held not to constitute obviousness[592]. As a general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out, the court concluded that Maniatis's teachings, in combination with Bohlen, failed to suggest the claimed invention, thus making the claimed invention not obvious.

The case concludes that the combination of a prior art reference teaching a method of gene cloning, together with a reference disclosing a partial amino acid sequence of a protein, would not render DNA and cDNA molecules encoding the protein obvious under section 103. It elucidates that existence of a general method of isolating gene sequences without specific reference to the protein in the claimed invention does not make the invention obvious. Furthermore, it also points out that existence of partial sequences does not make a longer sequence obvious. The case reiterates the principle in patent law that "Obvious to try" is not obviousness. It further points out that a prior art reference has to give rise to a complete conception in order to make the claimed invention obvious.

[589] Id. at 1559.
[590] Id.
[591] Id.
[592] Id.

The cases indicate that the standards of non-obviousness are complicated and flexible when it comes to genes or gene based inventions. While decisions are made on a case-by-case basis, certain principles can be crystallized from THE decisions of the courts. Principles for gene related inventions can be summarized as follows:

a. The combination of a prior art reference teaching a method of gene cloning, together with a reference disclosing a partial amino acid sequence of a protein, would not render DNA and cDNA molecules encoding the protein obvious under section 103.

b. Existence of a general method of isolating gene sequences without specific reference to the protein in the claimed invention does not make the invention obvious.

c. Existence of partial sequences in the prior art does not make a longer sequence obvious.

d. "Obvious to try" is not obviousness in gene related inventions as the field is fraught with uncertainty.

e. Obviousness requires reasonable predictability of success from the prior art in order to bring it outside the scope of 'Obvious to try' and make it obvious.
The maturity of the field is considered for such a determination through the eyes of a person with ordinary skill.

f. Existence of a prior art reference indicating expression of genes in one species does not make the expression of the genes in other species obvious.

g. Combination of a prior art reference disclosing a general method of isolating DNA sequences coding for proteins without reference to a specific protein combined with a partial sequence would not make the complete sequence obvious.
Homology with the gene sequence of other species and existence of general methods of isolating genes would not make an isolated gene sequence obvious.

h. Existence of discrete prior art with missing links would not make an invention obvious.

EUROPE

Article 52 of the European Patent Convention states that European patents shall be granted for any inventions which are new and which involve an inventive step and Article 56 provides 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[593]. Like in the US, an invention will have inventive step in Europe only if the invention is not obvious in the light of the prior art to a person with ordinary skill in the art. Tests for Determination of inventive step of genes and gene related inventions have been ambiguous due to uncertainty in the field. The European Patent Office and Boards have been striving to frame clear guidelines for determining inventive step in gene-based inventions. The decisions of various Boards in the European Patent Office indicates the uncertainty in 'inventive step' jurisprudence.

EPO Decisions

Relaxin Case[594].

The patentee had developed a process for obtaining H2-relaxin and the DNA encoding it, had characterised these products by their chemical structure and

[593] Article 52 and 56, Convention On The Grant Of European Patents (European Patent Convention) of 5 October 1973 text as amended by the act revising Article 63 EPC of 17 December 1991 and by decisions of the Administrative Council of the European Patent Organisation of 21 December 1978, 13 December 1994, 20 October 1995, 5 December 1996 and 10 December 1998.

[594] Howard Florey/Relaxin(Oppositions by Fraktion der Grunen Im Europaischen Parlament; Lannoye), Opposition Division, 8 December 1994, [1995] E.P.O.R. 541.

had found a use of the protein[595]. Opposition had been entered by the Fraktion der Grunen, and separately by their Fraktionsprasident (Paul Lannoye), under Articles 100(a) and (b)[596]. However, no prior art was cited in respect of the lack of inventive step and the closest state of the art for the subject matter of the claimed invention according to the opponents was the woman from whom the mRNA used to prepare the H2-relaxin cDNA was isolated[597].

The Board pointed out that as the proprietor was not preparing a known substance by conventional means, but providing to the public for the first time a product whose existence was previously unknown, the claimed invention is regarded as inventive whatever the methods used to prepare the product[598]. The Board stated that the claims are considered to involve an inventive step because there is no pertinent real prior art available rendering the claimed subject matter obvious[599].

R. v. GENENTECH[600]

The patent was concerned with interferon-gamma and the DNA sequence coding for it. It was challenged on the ground that it lacked inventive step based on certain prior art references.

The board stated that from the prior art references, the skilled person knew that all attempts of stimulation of lymphocytes, purification and

[595] Id.
[596] Id.
[597] Id.
[598] Id. at 548.
[599] Id.
[600] R. v. GENENTECH/HIF-Gamma, Technical Board of Appeal 3.3.2, July 20, 1993 [FN1], [2003] E.P.O.R. 12.

characterisation of the desired interferon-gamma were not sufficient to provide the protein in a quantity and quality which would have put him in a position to identify unambiguously the substance as such, let alone to provide a sufficient amount of it for medical purposes[601]. As a considerably greater number of genes had been made the subject of cloning and expressing methods, and skills and experience in this technical field were developing rapidly In October 1981, the Board stated that the knowledge of the notional skilled person in the art must be considered as that of a team of the appropriate specialists, who know all the difficulties still to be expected when considering cloning a new gene[602]. The Board further stated that the skilled person must be assumed to lack the inventive imagination to solve problems for which there do not exist already routine methods of solution, the appropriate comparison being not with a team but with a highly skilled technician carrying out a project where the initial instructions received are already adequate to tell the technician how to overcome any problems likely to arise[603]. It also stated that the notional skilled person, with a practical orientation, would have to weigh up carefully the amount of time and effort required by any technique in general against the probability of success that could reasonably be expected from it, in each case based on its own technical facts and without having to perform scientific research in areas not yet explored[604].

As a skilled person would be confronted with the situation that little was known about the protein as such and actually contradictory data had been published making the situation particularly confusing despite the fact that an improved stimulation method was known, as the quantity and quality of the mRNA available from this was extremely poor, making the prospects of success for the recombinant-DNA-technique route look very poor if nothing better than this known method could be found and as the decisive screening method was

[601] Id. at 109.
[602] Id.
[603] Id.
[604] Id.

not to be considered as a reliable way to find what could only be described as "a needle in a haystack", the Board was convinced that there is no sufficient certainty that the skilled person in this situation would have tried the patented method with any reasonable expectation of success[605]. In other words, the Board observed that while someone might have chosen the route of the recombinant-DNA-technique, he would only have attempted it despite success being very uncertain, for example because he trusted in his own luck, skill and inventive ingenuity to overcome the known and the as yet unknown problems involved, even though these problems were such that the average skilled person would expect to fail[606].

The Board remarked that it was common general knowledge at the time of priority that the cloning of each and every gene coding for a certain protein depends on many technical details which are particular to each single gene, for example the size, the existence or non-existence of introns or pre- or pro-sequences and the existence and location of necessary restriction enzyme sites[607].

So, the Board reasoned that a reasonable extrapolation from the successful cloning of one gene to another was, therefore, only in rare cases possible[608]. The Board stated that the goal of the inventors 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[609]. By identifying the DNA-sequence, the Board observed that the inventors provided a guide rope to the peak which enabled others to be certain of getting to the same peak with much less trouble[610]. As the appellants failed to show that a route, which involved

[605] Id.
[606] Id. at 110.
[607] Id.
[608] Id.
[609] Id.
[610] Id.

no invention, could have reached the peak the Board concluded that the invention possessed inventive step[611].

The case lays down the following principles:

a. Inventive step is assessed based on reasonable likelihood of success, which depends on the level of knowledge about the field.
b. The cloning of each and every gene coding for a certain protein depends on many technical details which are particular to each single gene, for example the size, the existence or non-existence of introns or pre- or pro- sequences and the existence and location of necessary restriction enzyme sites that knowledge of general cloning techniques cannot make the invention obvious.
c. Skilled person in the art must be considered as that of a team of the appropriate specialists, who know all the difficulties still to be expected when considering cloning a new gene.
d. The skilled person must be assumed to lack the inventive imagination to solve problems for which there do not exist already routine methods of solution.
e. Success that could reasonably be expected from a method of cloning in each case based on its own technical facts and without having to perform scientific research in areas not yet explored is a factor for determining inventive step.
f. Existence of a routine technique would not make a specific method of isolating a DNA sequence obvious.

R. v. British Technology Group[612]

The patent at issue covers two main alternative embodiments, namely (a) a DNA encoding an F polypeptide or (b) a DNA encoding a HN polypeptide of

[611] Id.
[612] R. v. British Technology Group/Newcastle disease virus, T 145/95, Technical Board of Appeal 3.3.4, September 30, 1998, [2003] E.P.O.R. 42.

Newcastle disease virus Beaudette C strain[613]. The patent was revoked by the Opposition Division for lack of inventive step over three prior art references taken in combination with the general technical knowledge of the various recombinant DNA techniques for cloning and expressing a viral gene[614].

The Board discussed the inventive step involved in HN polypeptide. In the board's judgment, the closest prior art with respect to this embodiment was a copy exhibited at a meeting of the Biochemical Society at Oxford, England on July 17, 1985[615]. The poster, without giving any nucleotide sequence information, reported the results of work in connection with the cloning of the HN and F genes of NDV[616]. The board started its analysis by observing that when evaluating inventive step, the skilled person is assumed to be aware of the totality of the prior art pertinent to the relevant area of technology, i.e. of everything made available to the public by any means[617]. As the poster was pertinent to the technical area of NDV gene technology, in particular to the cloning of the NDV glycoprotein genes, and contained information addressed to the person skilled in the art, the board stated that he or she would have taken this disclosure into account when working at the cloning of NDV genes[618].

Furthermore, as the poster outlined the essential experimental steps which had led the authors to the cloning inter alia of the HN gene of NDV, which involved techniques well known in themselves with which the skilled person in 1985 was quite familiar and as the further data reported in the poster presentation (order of the genes, presence of the sequence downstream from the open reading frame of the HN gene, the 69-residues amino acid sequence at the C-terminus and the high homology with the corresponding sequence of SV5) would have provided further means for checking the results obtained, the

[613] Id.
[614] Id.
[615] Id. at 395.
[616] Id.
[617] Id. at 396.
[618] Id. at 397.

board stated that the information would have given the skilled person a reasonable expectation of obtaining clones with overlapping inserts of the NDV genome, in particular clones spanning the HN gene, as achieved by the authors of the poster presentation[619]. Thus, in the board's judgment, when working within the framework provided by the disclosure of poster, the skilled person did not need more than ordinary skill in order to arrive by known methods at a DNA sequence encoding a HN polypeptide[620]. As per the Board, it was merely a matter of filling the gap in information by using common general knowledge and routine skill, this being a task, which could be performed by the skilled person[621]. As the repetition of the work in the prior art reference would only have required a feasible amount of experimentation in an area already explored, the board concluded that it does not require undue burden or skill out of the ordinary to carry out the invention[622]. The Board further stated that the presence in the description of the patent in suit of more experimental details than the poster disclosure did not necessarily mean that such disclosure was non-enabling for a person with ordinary skill to make it irrelevant for obviousness determination[623].

Because the general experimental outline provided in the patent was identical to that reported in poster and in the Board's view the skilled person would not have had to struggle unduly in order to repeat and complete the work described in the poster, the Board held that the claimed invention was not obvious[624].

The case elucidates that a prior art reference combined with the knowledge of a person can make an invention obvious even if the prior art reference has gaps

[619] Id. at 396.
[620] Id. at 398.
[621] Id.
[622] Id.
[623] Id.
[624] Id. at 399.

when compared to the claimed invention, if the knowledge of a person with ordinary skill and maturity of the field can fill such gaps.

Decision T207/94[625]

The claimed invention was directed to a recombinant DNA molecule capable of inducing the expression in a unicellular host of a polypeptide displaying the immunological or biological activity of human beta-interferon ("beta-IFN"), the molecule being selected from a group of three specified plasmids or DNA variants of the same[626]. The Opposition Division held that the claimed invention had inventive step. On appeal, the board revoked the decision of the opposition division for lack of inventive step.

The board started its analysis by pointing out the closest prior art, which discloses the cloning of beta-IFN cDNA as well as its sequence[627]. The Board stated that the objective technical problem to be solved based on the prior art was the recombinant production of a polypeptide displaying immunological or biological activity of human beta-IFN, which had been solved by the claimed invention[628]. In the Board's judgment, the state of the prior art implies that the insertion of the beta-IFN coding sequence downstream of a promoter so that it would be transcribed from its promoter and subsequently translated in an active form was prima facie considered quite feasible from the point of view of a person with ordinary skill[629]. Based on the state of the art, the Board concluded that the construction of the beta-IFN expression vector per se, using promoter systems known to work in the prior art, would not require more than

[625] BIOGEN/Human Beta-interferon(Opposition by Schering), T207/94, Technical Board of Appeal 3.3.4, April 8, 1997, [1999] E.P.O.R. 451.
[626] Id.
[627] Id. at 462.
[628] Id.
[629] Id. at 463.

routine work from the average skilled person, thus making the invention obvious[630].

The Board went on to point out that "the hope to succeed" should not be misconstrued as "a reasonable expectation of success"[631] In the Board's judgment, the former is the mere expression of a wish whereas the latter requires a scientific evaluation of the facts at hand[632]. In the case of gene expression, the Board observed that scientific evaluation necessitates that the properties of the expression partners (the gene be expressed and its protein product on the one hand, and the recombinant host on the other) be compared[633]. It further pointed out that if any one of them has properties which common general knowledge at the priority date would have suggested might be unfavourable to their relation-ship, it is justified to conclude that the person skilled in the art would have had no reasonable expectation of success[634]. Furthermore, in the Board's view, 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 this invention could not be achieved, nor that it could[635].

Though the known features of beta-IFN would necessarily have been regarded as insurmountable obstacles for its expression in recombinant form in the light of prior art, the Board stated that it would not be enough to rebut a reasonable likelihood of success[636]. Rather, to the Board, the skilled person would consider the knowledge of the properties of beta-IFN as an asset in identifying in the light of the state of the art which problems, if any, such properties may cause and which solutions were available[637]. By doing so, the board was of the view

[630] Id.
[631] Id.
[632] Id.
[633] Id.
[634] Id.
[635] Id.
[636] Id. at 464.
[637] Id.

that the skilled person would come to the conclusion that the properties of beta-IFN were not such as to bar the way to its expression[638]. In the light of the aforementioned reasoning, the Board held that the claimed invention lacked inventive step.

This case elucidates that if a claimed invention would have been carried out by a person with ordinary skill through plain routine work, it would be obvious. Reasonable expectation of success to make an invention obvious, requires a scientific evaluation of the facts, which requires comparison of properties of the expression partners in the case of gene expression. The fact that there are insurmountable obstacles to carry out an invention will not make the invention non-obvious.

Genentech Decision[639]

The patent was concerned broadly with the construction of DNA vectors suitable for use in expressing exogenous genes in yeast and had been revoked by the Opposition Division for breaches of Article 123 and lack of inventive step having regard to an oral disclosure at the 10th International Conference of Yeast Genetics and Molecular Biology[640]. The prior art was represented by the totality of the disclosure made by Dr Guarente at the 10th International Conference, including the advance abstract, the subsequent paper, the poster presentation and workshop discussions[641]. It was perceived at the conference that Dr Guarente had provided by his oral disclosure the first demonstration of the expression in yeast of a sequence exogenous thereto under the control of a yeast gene promoter[642].

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[638] Id.
[639] Genentech/Expression In Yeast(Oppositions by Boehringer Mannheim; Chiron; Celltech; Zymogenetics; Delta Biotechnology; Takeda; Novo; Gist- Brocades; Behringwerke; Ciba-Geigy), Technical Board of Appeal 3.3.2, 20 June 1994, [1996] E.P.O.R. 85.
[640] Id.
[641] Id.
[642] Id.

The Board started its analysis by stating that it is the normal task of the skilled person to be constantly occupied with the elimination of deficiencies, with the overcoming of drawbacks and with the achievement of improvements of known devices and/or products[643]. In the Board's view, the skilled person in this field is well aware of the fact that even a small structural change in a product (for example a vector, a protein, a DNA sequence) or in a procedure (for example a purification process) can produce dramatic functional changes[644]. Therefore, the said expert would constantly be conditioned by the prior art and, before taking action, would carefully ponder any possible modification, change or adjustment against the background of the existing knowledge[645]. In particular the board pointed out that the skilled person working in one field (for example expression in yeast) would regard a means conveniently adopted in a neighbouring field (for example the bacterial art) as being readily usable also in that field, if this transfer of technical knowledge involves nothing out of the ordinary[646]. The board observed that it should be borne in mind that the skilled person in the field of expression of polypeptides in yeast had good reasons to move in the direction of the technical teaching of the patent-in-suit, because the skilled person knew how to adjust the technical teaching from an adjacent neighbouring field, namely the bacterial art[647]. So, the board pointed out that this was a sufficient incentive for an expert at least to try to transform knowledge from the bacterial art to yeast. And observed that in this respect the expert in the bacterial art and for yeast is the same[648].

In the Board's view, the structural change which makes the difference between the vector of the claimed invention and the empty plasmid is one that a skilled person occupied with the construction of alternative yeast expression vectors

[643] Id. at 97.
[644] Id.
[645] Id.
[646] Id.
[647] Id.
[648] Id.

would have readily considered[649]. As per the Board, the introduction of such a change into the known plasmid vector required for a skilled person nothing out of the ordinary and thus involved no inventive skill, all being a matter of technical convenience[650]. Consequently, the Board believed that the skilled person on the basis of the teaching of the prior art reference would not have regarded the region immediately preceding the start signal of a yeast gene (the 5' untranslated leader region) as being "sacrosanct" or "untouchable" in spite of alleged uncertainties about a possible function of the leader sequence[651]. The board reasoned that the fact that the introduction of point mutations had not sensibly changed translation efficiency but rather indicated that alterations therein were feasible[652]. In the light of the reasoning, the Board concluded that it would have been obvious for a skilled person to try with a reasonable expectation of success to modify the loaded plasmid by producing one or more deletions into the 5' untranslated leader sequence of the yeast gene which afforded the promoter[653].

In view of the prior art the Board stated that the skilled person would have regarded the modification as feasible and as involving only fully calculable risks, if any[654]. Thereby, the Board concluded that the skilled person would have readily arrived at a yeast vector and at its use for expressing an exogenous polypeptide in yeast as in the claimed invention[655]. The Board observed that the claimed invention was a matter of normal design procedures for which neither "creative thinking" nor "inventive talent" was necessary[656]. For the above reasons, the Board concluded that claimed invention lacks an inventive step.

[649] Id. at 98.
[650] Id.
[651] Id.
[652] Id.
[653] Id.
[654] Id. at 99.
[655] Id.
[656] Id.

The Board in this case discussed the role of a skilled person in determining the reasonable likelihood of success. It stated that a skilled person is generally cautious in applying unexplored knowledge. However, it held that it would not be difficult for a skilled person to apply knowledge from the field of bacteria to yeast, if the transfer of technical knowledge involves nothing out of the ordinary. So, if the transfer of knowledge from one field to another requires nothing out of the ordinary, an invention, which is based on such a transfer, would be obvious.

R. v. Chiron[657]

The patent in issue was directed to a DNA molecule comprising a specified nucleotide sequence encoding insulin-like growth factor II (IGF-II)[658]. The patent had been revoked by the Opposition Division for lack of inventive step on the basis that the skilled person would have inevitably arrived at the claimed DNA by merely applying the teachings of the prior art reference to the screening of the cDNA encoding IGF-II[659].

As per the Board, the closest prior art for the claimed subject matter was concerned with proteins belonging to the "insulin gene family" (IGF), comprising insulin, IGF-I, IGF-II and relaxin[660]. The prior art reference deals with the same problem as the patent in suit, namely the problem of looking for the gene encoding IGF-II and conveys on the skilled person the incentive to look for the desired DNA[661]. In the light of the prior art reference, the Board concluded that the claimed invention lacked inventive step. The Board observed that the disclosure of the correct amino acid sequence by the prior art reference is not important because amino acid sequence information about IGF-II had been

[657] R. v. Chiron/IGF-II, T475/93,Technical Board of Appeal 3.3.4, July 17, 1997 [FN1], [2003] E.P.O.R. 48.
[658] Id.
[659] Id.
[660] Id. at 441.
[661] Id.at 442.

available to the skilled person since 1978 from other sources, which would be enough to enable them to come up with the claimed invention[662].

The Board stated that an inventive step for the claimed sequence may follow from the selection of this sequence among a great many other possible allelic DNA sequences, if said selection brings about an unexpected advantageous effect, eg. As in the instance a higher expression is achieved with the claimed DNA than with any other allelic DNA[663]. It said that the patent holder had not provided any evidence showing that in the present case such a selection occurred, let alone any evidence of the unexpected advantageous effect[664].

In the technical circumstances given in the light of the disclosure in the prior art reference, the Board stated that the only blockage that could have prevented the skilled person to try cloning the gene encoding IGF-II could have been a possible low expectation of being successful[665]. The board stated that the patent holder failed to show a low expectation of success by the skilled person, once the screening methods available before the priority date of the patent in suit were put into practice in an attempt to isolate from a library a gene encoding IGF-II[666]. The Board was convinced that the cloning of the IGF-II DNA by using the technique of the second prior art reference did not require to overcome additional difficulties in comparison with the cloning of the DNA encoding IGF-I that could have arisen when trying to put into practice the approach described in the claimed invention[667]. Moreover, the board brushed aside patent holder's on reasonable expectation of success by stating that the facts put forward would not have lowered the skilled person's expectation of success in isolating the DNA coding for the IGF-II protein by applying the

[662] Id.at 442.
[663] Id.
[664] Id.
[665] Id. at 443.
[666] Id. at 443.
[667] Id. at 444.

technique disclosed in the second prior art reference[668]. Finally, the Board stated that Dr. Rall's and Prof. Bell's expert testimony indicates failure to isolate the gene encoding IGF-I by using low degeneracy probes due to selection of the wrong house library and not because of difficulty in carrying out the invention[669].Based on the aforementioned reasoning, the Board concluded that the subject matter of the claimed invention does not involve an inventive step.

The case laid down that an invention would lack inventive step even if the prior art reference lacks complete description provided the reference can be supplemented by information available to a person with ordinary skill in the art. Reasonable likelihood of success can make an invention obvious and showing low expectation of success can rebut it. Reasonable likelihood of success can be proved by prior art information, experiments, expert testimony and so on.

Mycogen Decision[670]

The patent was directed to a method for genetically modifying a plant cell by transferring into it a combination T-DNA/plant promoter gene such that expression of the protein encoded by the plant structural gene was detectable in the plant cell[671]. The patent was opposed by 11 opponents on the grounds of lack of novelty and lack of inventive step over the disclosure of the method at a theoretical level in the prior art for the expression of the protein phaseolin.

The Board stated that as per the closest prior art for the claimed invention at issue, the technical problem to be solved was the achievement of detectable levels of expression of phaseolin in a dicotyledonous plant cell, which problem

[668] Id.
[669] Id.
[670] MYCOGEN/Modifying Plant Cells(Oppositions by Unilever, Centerns, Sandoz, Monsanto & Max Planck Institute), T694/92,Technical Board of Appeal 3.3.4, May 8, 1996, [1998] E.P.O.R. 114.
[671] Id.

was solved by the claimed invention[672]. The Board started its analysis by pointing out that a reasonable expectation of success" should not be confused with the understandable hope to succeed[673]. The Board stated that while it can be said that, in the light of a prior art reference, the experiment in question was "obvious to try" for the skilled person, it was not necessarily true that the person would have had any reasonable expectation of success when embarking on it[674].

As the outcome of the said experiment was still uncertain, the board observed that the question to be decided was therefore whether the average skilled person was in a position to reasonably predict its successful conclusion, on the basis of the existing knowledge, before starting an experiment[675]. The Board was of the view that in early 1983 the art of genetically modifying plant cells so as to achieve detectable levels of expression of a transferred foreign gene was not yet routinely established[676]. Although some success had been reported in respect of T-DNA vector constructs where the foreign gene was placed under the control of Ti promoters, the board pointed out that the skilled person still faced a number of uncertainties and problems, such as stability of alien DNA into T-DNA and into the plant genome, presence of introns, stability of the proteins, effects of regulatory controls, etc[677]. In the light of such uncertainties, the Board stated that the claimed invention could not be easily carried out by a person with ordinary skill and therefore lacked inventive step. As all the scientific factors and considerations would have negatively influenced the degree of confidence of the skilled person, the board pointed out that he or she would therefore not have reasonably expected that expression of detectable levels of phaseolin in a dicotyledonous plant cell would be easily achievable and, owing to this, would have come up with the

[672] Id. at 126.
[673] Id.
[674] Id.
[675] Id. at 127.
[676] Id.
[677] Id.

results of the patent in suit[678].Based on the reasoning the board concluded that the subject matter of the claimed invention involves an inventive step

The case points out that hope of succeeding would not be enough to prove reasonable likelihood of success for purposes of inventive step. Obvious to try would not be considered to be obviousness. Existence of uncertainties in the field in carrying out an invention from the point of view of a person skilled in the art would make the invention non-obvious.

R. v. FUJISAWA/A[679]

The patent was directed to a process for the production of Alpha-human atrial natriuretic polypeptide ("Alpha-h ANP")[680]. The Opposition Division revoked the patent on the grounds of lack of inventive step having regard to the prior art knowledge about the nucleotide sequences encoding Alpha-h ANP in combination with the general teaching in the prior art about the expression of heterologous proteins in a recombinant system in a fused, cleavable form[681].

The Board stated that while making an assessment of the prior art documents, it had to have regard to the particular circumstances and to decide the weight to be attached to each of them accordingly[682]. As per the Board, the closest prior art is represented by the disclosure at the 7th Annual Meeting of Molecular Biology Society of Japan of the expression of hANF as a fusion protein with TrpE in E. coli[683]. As regards the weight to be attached to the disclosure of the prior art reference the Board observed that while evaluating inventive step, the skilled person is assumed to be aware of the totality of the prior art pertinent to the relevant area of technology, i.e. of everything made available

[678] Id. at 128.
[679] R. v. FUJISAWA/Alpha-human ANP, T202/95, Technical Board of Appeal 3.3.4, July 21, 1998 [FN1], [2002] E.P.O.R. 4.
[680] Id.
[681] Id.
[682] Id.
[683] Id. at 40.

to the public by any means[684]. Though the prior art was described in a document, which was published after the priority date, the board stated that it was a true account of a presentation given before the priority date, which makes it relevant for determination of inventive step[685].

The Board observed that despite the reported failures in relation to some of the experiments, the skilled person would not have been deterred from using the method described in the prior art[686]. It went on to state that the claimed invention lacked inventive step because on the basis of the prior art the skilled person would have understood that there was a reasonable expectation of success in producing Alpha-h ANP from employing fusion proteins and the Lys-API cleavage[687]. In the Board's judgment, the skilled person looking for an alternative fused form of alpha-hANP did not need more than ordinary skill in order to arrive at the solution proposed in the claims at issue. His or her knowledge of the protein fusion technology and the disclosure of prior art reference would have readily suggested choosing Lys as a link to alpha-hANP and Lys-specific proteolysis as a feasible means for obtaining an intact alpha-hANP from the fused intermediate protein[688]. As per the Board the construction of such fused protein and of the corresponding gene implied merely the association of known elements, all working in a normal way, according to a known scheme with a reasonable expectation of success[689]. In the light of the reasoning, the board concluded that the claimed invention lacks inventive step.

The case points out that the date of a prior art reference plays an important role in determining the obviousness of an invention. Furthermore, it provides that existence of a prior art reference combined with knowledge of a person

[684] Id. at 42.
[685] Id.
[686] Id.
[687] Id. at 42.
[688] Id.
[689] Id.

with ordinary skill would make an invention obvious, if the combination gives rise to reasonable likelihood of success for making the invention.

Decision T886/91[690]

The patent related generally to a method for the recombinant production of polypeptides displaying HBV antigenicity, and means therefor, including specific deposited recombinant DNA molecules[691]. It was challenged on the ground that it lacked novelty and inventive step. The Board stated that the claimed invention possessed novelty but lacked inventive step, since it would have readily occurred to the skilled person to try to complete the work described in a prior art reference by identifying and characterising the primary structure of the DNA sequences encoding HBsAg and HBcAg within the said fragments of the genome of HBV serotype adyw and to express them in a recombinant DNA system such as described in the prior art reference so as to produce antigenically active products[692]. The Board stated that the skilled person merely needed to proceed experimentally as in the prior art reference in the light of other prior art references[693]. It further stated that the expression of antigenically active products was to some extent feasible in a recombinant DNA system[694].

The case reiterates the fact that an invention would lack inventive step if a person with ordinary skill can carry out the invention by combining the cited prior art reference and knowledge in the field.

Unilever Decision[695]

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[690] BIOGEN/Hepatitis B Virus(Oppositions by Abbott; Takeda; Warcoin; Smith Kline Beecham; Institut Pasteur;Intervention by Medeva), T886/91,Technical Board of Appeal 3.3.2, June 16, 1994, [1999] E.P.O.R. 361.

[691] Id.

[692] Id.

[693] Id.

[694] Id.

[695] Unilever/Chymosin(Oppositions by Celltech; Hansens Laboratorium), T386/94,Technical Board of Appeal 3.3.4, January 11, 1996, [1997] E.P.O.R. 184.

The patent was concerned broadly with DNA molecules comprising the genes for preprochymosin and its maturation forms and micro-organisms transformed thereby[696]. It had been maintained by the Opposition Division in amended form in the face of 87 prior documents, of which one prior art reference was regarded as the closest prior art for purposes of assessing inventive step[697]. The closest reference disclosed chymosin as a precursor of prochymosin, and also the isolation in E. coli of a recombinant clone containing sufficient cDNA to code for 80 per cent of the prochymosin molecule[698].

The Board set aside the decision of the Opposition Division and revoked the patent based on lack of inventive step. The Board pointed out that in 1981, each step in the synthesis and cloning of cDNA could still be fraught with difficulties as obtaining large amounts of mRNA was quite difficult when the mRNA was naturally produced in low abundancy, the polymerising capacities of reverse transcriptase were not so optimised that mRNAs with big sizes were easily transcribed in full and the feasibility of devising efficient methods for the screening of the positive clones very much depended on the cDNA to be screened[699]. It stated that before embarking on the cloning and expression of the chymosin encoding DNA, the skilled person would carefully consider if any of these problems can be expected to occur[700]. As the teachings of the prior art reference lead to the conclusion that none of the difficulties expected from the prevailing knowledge on cDNA cloning would be encountered, the Board pointed out that the person skilled in the art would be fairly confident at the onset of the project that the combination of prior art teachings, and standard knowledge on biotechnological protocols would lead to the successful cloning of the genes encoding preprochymosin and its maturation forms. As at the date of priority, the cloning and expression of the chymosin DNA would have been perceived as an endeavour likely to succeed and that achieving this cloning did

[696] Id.
[697] Id.
[698] Id. at 194.
[699] Id. at 195.
[700] Id. at 195.

not pose such problems as to prove that this assumption was wrong, the Board concluded on this basis that the claimed invention lacks inventive step. The Board further stated that the cloning and expression of the chymosin DNA would therefore have been perceived by the skilled person as an endeavor likely to succeed; and achieving the cloning did not pose such problems as to deny this assumption[701]. It further pointed out that the fact that three other groups of workers started parallel development shortly after the patent holder cannot assist him to show inventive step[702]. In the light of it's reasoning, the board held that the claimed invention lacked inventive step.

The case lays down that non-existence of difficulties in carrying out an invention would deprive the invention of its inventive step.

Decision T500/91[703]

The patent relates to a recombinant DNA molecule for use in cloning a DNA sequence in bacteria, yeasts or animal cells[704]. The patent was challenged on the ground of lack of inventive step.

The Board started its reasoning by stating that on the priority date of the patent, only a limited number of persons were skilled in recombinant DNA-technology and that probably all of them were advanced senior scientists with skills above the average level in the broader art of biochemistry[705]. The Board then reiterated Decision T60/89, which held that the notional person skilled in the art of genetic engineering would not be defined as a Nobel Prize laureate,

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[701] Id.
[702] Id.
[703] Biogen/Alpha-Interferon II(Oppositions by Hoffmann la Roche; Upjohn; Boehringer Ingelheim Zentrale; Bender; Cetus; Hoechst; Boehringer Mannheim; Ciba-Geigy; Boehringer Ingelheim Pharma), T500/91, Technical Board of Appeal 3.3.2, 21 October 1992, [1995] E.P.O.R. 69.
[704] Id.
[705] Id. at 77.

but rather a graduate scientist or a team of scientists of that level of skill, working in laboratories which were developing genetic engineering techniques, in contrast to developing the science of molecular genetics, at the time in question (in that particular case around 1978)[706]. In other words, the Board stated that in accordance with the established jurisprudence of the Boards of Appeal, the notional skilled person who may be represented by a team of appropriate specialists oriented towards practicalities and the development of the art normally expected by him does not include solving technical problems by performing scientific research in areas not yet explored[707]. The Board observed that such a person skilled in the art, at the relevant date, would not have been able to isolate the desired DNA from any source containing it, albeit possibly in very low concentration, for example, from cDNA-mixtures obtained from mRNA-mixtures isolated from induced Namalva cells or leukocytes, solely by applying common general knowledge[708].

The Board went on to state that application of common general knowledge to the lawn gene bank does not result in the claimed invention[709]. In the Board's judgment, a skilled person could not reasonably expect that a procedure, similar to that published in prior art, would, by analogy, be a successful way to obtaining IFN-alpha by genetic engineering[710]. In the light of the available evidence and the proper definition of the activities, which can be expected from the notional person skilled in the art in the present situation, the Board concluded that there was no straightforward possibility of producing recombinant IFN-alpha on the basis of the disclosure of the prior art[711].

In the light of the analysis, the Board concluded that, having regard to the fact that the area of genetic engineering here under consideration was relatively

[706] Id.
[707] Id.
[708] Id.
[709] Id.
[710] Id. at 78.
[711] Id. at 79.

new at the relevant date, having further regard to the uncertainty at that date about facts influencing the success of the attempted recombinant-DNA techniques, and to the absence of a well-established general level of knowledge in this particular technical area, the present successful technical application of recombinant-DNA techniques, according to the claimed invention under consideration, involves an inventive step.

The case lays down that a person with ordinary skill in the art cannot be defined as a Nobel Prize laureate, but rather a graduate scientist or a team of scientists of that level of skill, working in laboratories which were developing genetic engineering techniques, in contrast to developing the science of molecular genetics. The level of ordinary skill varies from case to case and from time to time. A skilled person is not expected to solve problems through unexplored experiments. Inventive step is assessed by combining common knowledge with prior art references.

R. v. ALKO[712]

The claimed invention related to a DNA sequence which coded for the cellulase enzyme cellobiohydrolase II (CBH II) from Trichoderma reesei which is capable, when correctly combined with an expression vector, of expressing a protein having the cellulolytic activity of the said enzyme upon transformation of a host organism by the vector, the DNA sequence being one that coded for the specific aminoacid sequence recited in the Claim or for a substantially identical amino acid sequence showing the same enzymatic activity[713]. The examination division refused one of the claims for lack of inventive step over prior art documents and the patent applicant appealed[714]. The closest prior art

[712] R. v. ALKO/CBH II, T816/90,Technical Board of Appeal 3.3.2, September 7, 1993 [FN1], [2003] E.P.O.R. 45.
[713] Id.
[714] Id.

reference discloses the isolation in homogeneous form of CBH II from T.reesei and its partial physico-chemical characterisation[715].

The Board observed that the teaching of prior art references is limited to the cloning of DNA encoding CBH I and the expression of CBH I in a host cell is not disclosed[716]. It further observed that although the cloning of CBH II from T.reesei has been achieved by the appellant by way of a procedure which is largely similar to that disclosed in prior art references, nevertheless a modification has been introduced in the step of isolation of cellular RNA, namely "the grinding of frozen mycelia under liquid nitrogen", which modification is not derivable from the cited prior art[717]. Therefore, the Board reasoned that the patentee did not follow exactly the procedures known from prior art references because at least one modification has been introduced[718]. Moreover, the Board pointed out that the experimental work in the present case went few steps further since not only the cloning of the CBH II was achieved, but also its expression in yeast cells[719].

Even when it is possible to theoretically conceive a straightforward approach to solve a specific technical problem, the Board stated that the skilled person might be confronted with unexpected difficulties when trying to put the conceived strategy into practice[720]. It further stated that sometimes the difficulties can be overcome by introducing modifications in the known protocols, which can sometimes prove to be decisive for the successful conclusion of the research effort[721]. Though the available prior art offered undeniably good indications on how the underlying technical problem could be

[715] Id. at 418.
[716] Id.
[717] Id.
[718] Id. at 419.
[719] Id.
[720] Id.
[721] Id.

solved, the Board stated that the experimental approach successfully used by the patentee comprised a modification of the known procedure[722].

As per the Board, neither concrete evidence nor well-founded reasons were available to state that the said modification was unessential and that the skilled person would have achieved the cloning of CBH II merely by using the experimental approach of the prior art references in an analogous manner[723]. Under such circumstances, the Board conceded that the successful cloning and expression of CBH II was not merely a matter of routine adaptation of the known procedures[724].

In conclusion, as the prior art does not suggest that the skilled person would have arrived at a method for the production of CBH II of T. reesei in a recombinant system in a straightforward way, the Board held that the invention lacked inventive step.

The case lays down that existence of a modification in an invention, which is different from the prior art and which cannot be conceived by a person with ordinary skill in the art makes the invention non-obvious.

Biogen Decision[725]

The patent in suit was broadly concerned with providing an improved route through recombinant DNA technology to certain types of interferons[726]. The patent had been revoked by the Opposition Division on the ground of inventive step among other grounds[727]. The Opposition Division held a couple of claims

[722] Id.
[723] Id. at 420.
[724] Id.
[725] Biogen/Recombinant Dna(Oppositions by Hoffmann la Roche; Upjohn; Boehringer Ingelheim Zentrale; Bender; Cetus; Hoechst; Boehringer Mannheim, T301/87, Technical Board of Appeal 3.3.2, 16 February 1989, [1990] E.P.O.R. 190.
[726] Id.
[727] Id.

obvious in the light of the teaching of a document, which represents an article on synthesis in E. coli of a polypeptide with human leukocyte interferon activity published in Nature on 27 March 1980 under participation of, among others, Charles Weissmann, who is the inventor in the present case[728]. The document is generally referred to as Nagata after the name of one of the authors[729].

As the article was published after the priority date of the patent application, the board held that it is not relevant for obviousness determination[730]. The Board further stated that even if Nagata were to be considered as prior art, it would not deprive the claimed invention of its inventive step because the claimed invention has technical effect over and above Nagata[731]. The board stated that in the light of Nagata, it could certainly not have been expected that the Hif-II-206 fragment is the precursor for an additional valuable interferon-like protein, called IFN-<<alpha>>2 in the claimed invention[732]. When determining relative IFN activity by a procedure similar to that disclosed in Nagata, the board stated that IFN-<<alpha>>2 was about 30 times more active on human CCL23 cells than the structurally different IFN-<<alpha>> 1 disclosed by Nagata[733].

The modified plasmid, identified as Z-pBRT322(Pst)/HcIF- SN35-AHL6 in the claimed invention was considered by the Board as possessing unexpected properties in comparison with the starting plasmid Hif-SN35, known from Nagata[734]. The Board stated that hosts transformed with this modified plasmid, produce about 100 times more of a protein displaying activity of human leukocyte interferon as compared to hosts, transformed with unmodified Z-

[728] Id. at 205.
[729] Id.
[730] Id. at 207.
[731] Id.
[732] Id. at 210.
[733] Id.
[734] Id.

pBR322(Pst)/HcIF-SN35 known from Nagata[735]. In the light of this analysis, the Board concluded that the subject matter of the claimed invention has a technical effect and therefore an inventive step.

The case lays down that if an invention causes similar but improved effect to that mentioned in a prior art, it will not make the invention obvious as it involves a technical advancement that is responsible for the improved effect.

Decision T60/89[736]

The patent was concerned with a method of manufacturing a protein by recombinant DNA technology, comprising fusing the heterologous gene to a bacterial gene coding for a portion of a bacterial extra-cellular or periplasmatic carrier protein by a recombinant step so that the fused protein is excreted through a membrane of the cell within which it is made[737].

Setting aside the decision of the Opposition Division and maintaining the patent on the basis of the auxiliary request, the Board concluded that the skilled person in the field of genetic engineering in 1978 was not to be defined as a Nobel Prize laureate even though a number of workers in the field (including a co-inventor of the patent in suit) had attained that rank[738]. It further stated that the skilled person was to be regarded instead as the graduate scientist, or team of scientists, working in relevant laboratories[739]. The Board also provided that the level of skill to be imputed to the skilled person when considering inventive step is the same as that to be imputed when considering insufficiency[740].

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[735] Id.
[736] Harvard/Fusion Proteins(Oppositions by Hoechst; Unilever; Gist- Brocades), T60/89,Technical Board of Appeal 3.3.2, 31 August 1990, [1992] E.P.O.R. 320.
[737] Id.
[738] Id.
[739] Id.
[740] Id.

The following principles relating to inventive step can be deduced from the decisions of the European Patent Office:

a. A prior art reference combined with the knowledge of a person can make an invention obvious even if the prior art reference has gaps when compared to the claimed invention, if the knowledge of a person with ordinary skill and maturity of the field can fill such gaps.

b. Existence of a prior art reference combined with knowledge of a person with ordinary skill would make an invention obvious, if the combination gives rise to reasonable likelihood of success for making the invention.

c. Reasonable likelihood of success depends on maturity of the field.

d. Reasonable expectation of success to make an invention obvious, requires a scientific evaluation of the facts, which requires comparison of properties of the expression partners in the case of gene expression.

e. Hope of succeeding would not be enough to prove reasonable likelihood of success for purposes of inventive step.

F. Obvious to try would not be considered to be obviousness.

g. Existence of uncertainties in the field in carrying out an invention from the point of view of a person skilled in the art would make the invention non-obvious.

h. If a claimed invention would have been carried out by a person with ordinary skill through plain routine work, it would be obvious.

i. The fact that there are insurmountable obstacles to carry out an invention will not make the invention non-obvious.

k. j. An invention would lack inventive step even if the prior art reference lacks complete description provided the reference can be supplemented by information available to a person with ordinary skill in the art.

l. If the transfer of knowledge from one field to another requires nothing out of the ordinary, an invention, which is based on such a transfer, would be obvious.

m. The cloning of each and every gene coding for a certain protein depends on many technical details, which are particular to each single gene that knowledge of general cloning techniques cannot make the invention obvious.

n. Existence of a routine technique would not make a specific method of isolating a DNA sequence obvious.

n. Skilled person in the art must be considered as that of a team of the appropriate specialists, who know all the difficulties still to be expected when considering cloning a new gene.

o. The skilled person must be assumed to lack the inventive imagination to solve problems for which there do not exist already routine methods of solution.

p. A person with ordinary skill in the art cannot be defined as a Nobel Prize laureate, but rather a graduate scientist or a team of scientists of that level of skill, working in laboratories which were developing genetic engineering techniques, in contrast to developing the science of molecular genetics.

q. The level of ordinary skill varies from case to case and from time to time.

INDIA

Section 2(ja) of the Patent Act provides that "inventive step" means a feature of an invention that involves technical advance as compared to the existing knowledge or having economic significance or both and that makes the invention not obvious, to a person skilled in the art[741]. To satisfy the requirement of inventive step, an invention should either have a technical advance or economic significance. Furthermore, the invention should not be obvious to a person with ordinary skill in the art. Due to the dearth of case law and legislative history, the meaning of technical advance and economic significance is not clear. Based on the Manual, it can be interpreted that isolated gene sequences will be considered to have an inventive step in the light of their naturally existing counter parts. As the Indian Law gives importance to economic significance in the determination of inventive step, it would be easy for gene based inventions to satisfy this requirement because most gene sequences and related inventions have great significance in the biopharma sector because of the multitude of uses they can be put to. Due to the importance given to economic value of an invention, it appears that genes based inventions would pass through the inventive step much easily in India than in USA or Europe, which do not give primary importance to commercial value of an invention.

Public/Patent Domain Analysis

Non-obviousness requirement has lot of similarities under United States and European patent laws when it comes to gene based inventions. Both consider that existence of a general method of cloning would not make isolation of a specific sequence obvious. They consider that reasonable expectation or predictability of success from the point of view of a skilled person combined with maturity of the field is an important factor in determining obviousness.

[741] Section 2(j)(a), Indian Patent Act, 1970 as amended in 1999 and 2002.

Due to uncertainties in the field of genetic engineering, Obvious to try is not considered to be obviousness in both jurisdictions. Furthermore, existence of a gene in a gene bank would not make the isolation of the gene sequence obvious in both countries.

Having said that, the US Law provides that existence of a prior art reference indicating expression of genes in one species does not make the expression of the genes in other species obvious, while under the European law, such an expression would be obvious if it can be perceived by a person with ordinary skill. Furthermore, homology with the gene sequence of other species and existence of general methods of isolating genes would not make an isolated gene sequence obvious in USA but in Europe such isolation would be obvious if it can be expected by a person with ordinary skill.

Comparative study

The trilateral project taken up by USPTO, EPO and JPO dealt with inventive step in biotechnology inventions, which specific emphasis on gene based inventions. The cases cited in the report indicate the differences in the practices relating to non-obviousness of gene-based inventions in the patent offices.

Cases

1. Y is a structural gene encoding a functional polypeptide, the whole sequence of which is disclosed. Y1 is a partial DNA fragment of Y

As per the USPTO, the information contained in the specification must be assessed in the light of the entire prior art and there is no straightforward

answer for non-obviousness[742]. According to the EPO, the invention has no inventive step as it is merely a normal and common procedure for a person skilled in the art to obtain a partial DNA sequence on the provision that the corresponding whole sequence of the structural gene has been known from the prior art[743]; However, the EPO stated that a DNA fragment encoding a protein having some unexpected property vis a vis the known protein may be acknowledged as inventive[744].

2. Y1 is a certain DNA sequence encoding an allelic mutant of human protein X, which has several different codons from specific DNA sequences described in prior art (Y).

As in the earlier case, the USPTO requires an analysis of the specification in the light of the prior art to assess inventive step[745]. In EPO, the invention would lack inventive step because it is a common practice in the field of technology[746]. However, EPO states that when the obtained specific DNA has an effect, which is either qualitatively different from that of prior art or qualitatively homogeneous, but quantitatively superior, inventive step is present if a person skilled in the art cannot expect this effect on the basis of the state of the art[747].

3. Y1 is a DNA encoding human protein X, the function and the sequence of which are similar to that in prior art (Y).

Once again, like in the earlier cases, the USPTO requires to analyze the specification in the light of entire prior art to make a non-obviousness

[742] Id.
[743] Id.
[744] Id.
[745] Id.
[746] Id.
[747] Id.

determination[748]. On the other hand, EPO states that the invention usually lacks inventive step because it is a common practice in the field of technology[749]. The EPO takes the view that a DNA encoding human protein X may exceptionally be considered to involve an inventive step if there was a prejudice in the art against the cloning of the human DNA encoding protein X and/or the applicant provided clear evidence that the mere employment of conventional techniques of molecular biology and recombinant DNA technology would not have resulted in the isolation of the claimed human DNA[750].

4. Y is a partial amino acid sequence of protein X. Y1 is a DNA sequence encoding protein X

The USPTO explains that obviousness is a very fact-dependent determination which must be made in every application, based on the facts of that case and the state of the prior art at the time of the filing; no per se rules of obviousness exist. On the other hand, EPO gives negative answer, even though no partial amino acid sequence of protein X has been disclosed in the prior art but protein X was described in a highly purified form which would make it possible for a skilled person to sequence protein X.

Though there are certain similarities among non-obviousness criteria in USA and Europe, the comparative study and analysis indicates that there are certain important differences. While isolating a partial DNA sequence would not be non-obvious in the light of the full sequence and while a full sequence in the light of a partial sequence would not be non-obvious except in rare circumstances in Europe, such inventions might be non-obvious in the light of prior art in USA. The cases in the comparative study indicate that the US patent law relating to non-obviousness is much flexible when compared to the

[748] Id.
[749] Id.
[750] Id.

European law. Therefore, when it comes to gene based inventions it would be easy to pass through the non-obviousness filter in USA than in Europe.

As a result the non-obviousness requirement defines a larger patent domain and smaller public domain of genetic inventions in USA when compared to Europe. Due to lack of interpretation in the Indian law, the position under Indian Law is very unclear. However, as India gives equal importance to technical advance and economic significance, it can be said that the Indian non-obviousness requirement is more flexible than that in USA and Europe, this making it easy for gene based inventions to pass through easily in India than in USA and Europe. Based on this analysis, it can be said that the size of patent domain is larger and public domain smaller in India than in USA and Europe.