The Patentability and Protection of DNA-based Inventions in the EPO and the European Union

DR DENIS SCHERTENLEIB

One of the principal aims of patents is to promote competition and scientific progress through the commercialisation of technologies. Nevertheless, patents are fundamentally anticompetitive and great care is needed for an acceptable balance to be found between the promotion of competition and the protection of intellectual property rights.

Biotechnology is a recent development brought on by discoveries in molecular biology during the last fifty years. Each new technology has necessitated modifications to the law. The first patents, during the Industrial Revolution, were concerned mostly with mechanical devices. When chemistry developed, the case law refined the legal framework to solve the new problems posed.

Again we are faced with a new technology. Its complexity, however, poses problems which could never have been envisaged when patent law developed. Typically, the subject-matter of biotechnology patents is the building blocks of life and processes to modify it. Never has the subject-matter of patents been so far-reaching or the promises of the new technology so great.

Aware of that fact, the European Union has issued a Directive on biotechnology to clarify the issues. While this is welcome progress, it has generated questions of its own. The Trilateral Projects between the EPO, JPO and USPTO have attempted to clarify their respective doctrines further.

This article will discuss the current EPO and EU stance on the patenting of DNA-based inventions. First will be considered, in the context of DNA, the major criteria for patentability, namely novelty, industrial applicability, inventiveness and the further requirements for patent applications: unity, enablement and clarity. Then will be considered their consequences for the patentability of such inventions and the potential problems with the current doctrine.

Technical Background

The subject of biotechnology patent law is rife with technical terms. Some important distinctions are often overlooked while new terminologies often conceal limited inventions. For instance ESTs are merely fragments of genes which can be put to only very limited technical uses. Yet the patent applications and case comments could induce one to believe that they are of even greater technical importance than full-length genes.

It is necessary briefly to run through the basics of the science underlying this technology as the law cannot be separated from it.

DNA in its natural state

All DNA in multicellular organisms is found within a few chromosomes. Each of these carries thousands of genes organised randomly along its length. There is no separation between the genes and they read as one continuous sequence. It is only the operation of control sequences which separates the chromosomes into regions we call genes. Genes themselves consist of, firstly, promoter regions which control their activation in time and within cells in the organism and, secondly, the coding region which will specify the structure of the protein coded by the gene. The first step in gene expression is the transcription of the genomic DNA into messenger RNA (mRNA). The sequence is conserved but large chunks of the original genomic sequence (introns), including the promoter, are removed, leaving only parts of the sequence called exons. There is considerable variation in the uses of the exon sequences and some genes could produce up to 25000 different proteins by combinatorial splicing. Only parts of the messenger RNA are then translated into a protein. It is the genetic code which specifies which amino acids are added to the protein based on the mRNA sequence. The genetic code is, however, degenerate, meaning that several different sequences of DNA can code for the same protein so that the protein sequence does not enable one to extrapolate its original DNA sequence. Again, different parts of the mRNA can be translated and the resultant protein can vary in size and thus in function. The new protein is then folded, chemically modified and its final conformation and structure cannot be predicted reliably from its sequence.

Cloning genes

Clones of a gene can be either of genomic DNA (incorporating promoters and intron sequences) or of cDNA (complementary DNA matching the sequence of the mRNA). To prepare genomic clones, genomic DNA is randomly cut and fragments are inserted into bacterial plasmids (being small bacterial chromosomes) and replicated in bacterial cultures so as to obtain a multitude of bacteria each carrying a different fragment. Cloning cDNA is more involved as there is never a DNA sequence matching the sequence of mRNA in nature (because in nature DNA is always genomic and thus contains sequences absent from mRNA). The cDNA must be reverse-transcribed from the mRNA using man-made techniques. Once the cDNA is obtained, the fragments are cloned into bacterial plasmids as above. The result is a new construct of DNA missing all the regulatory

sequences and the introns of genomic DNA. It is possible to translate such cDNA into proteins as the introns and promoters do not participate in specifying the protein sequence. There is, however, no guarantee that the sequence for the whole protein was cloned and only a fragment could have been obtained. Such incomplete sequences are called ESTs and their only function is as probes to obtain the full-length sequence or to localise mRNA transcripts.

Bioinformatics

Through the advent of computing power, it has been possible to compare newly found sequences with old ones by homology searches. As the sequence of DNA specifies the sequence of amino acids in a protein, it is possible to predict the amino acid sequence of a protein coded by cDNA. If two proteins share similar sequences across regions then it is likely that they will have similar structure and properties. Bioinformatics looks for similarities. However these are just guesses; nothing is known about further modifications such as the three-dimensional folding of the protein and the further biochemical alterations to it.

Bioinformatics only assigns genes to a very broad class of functions but not their real cellular functions. It is possible to guess that a protein is regulating DNA transcription or that it is part of some signalling pathway, but one still does not know what it regulates or what it signals; merely that it has the potential to perform such broad functions if it were to fold and be processed like other proteins of similar sequence. Protein families evolve by duplication, mutation and the exchange of whole functional domains. Therefore homology between different proteins at least across sub-regions is common because it is a common evolutionary process. Immunoglobulin receptors involved in immunity share sequence similarities with various cell signalling receptors which are involved in nervous system development such as nerve growth factor. Their structures may show similarities but their functions differ.

To hold that the function of a protein can be determined by computer studies without actual experimentation is inaccurate and results from a misunderstanding of what bioinformatics actually performs.

Novelty

Patents on genes have been criticised on many grounds. A prevalent complaint is that genes are naturally occurring entities existing in living organisms and thus are not invented but discovered. This argument does not hold in science or in law. The DNA sequences used by biologists have never existed in that form before and are always modified to an appreciable extent. The DNA we use is created and not discovered. The law has recognised this scientific fact for some time. To hold otherwise would have been atypical as many patents have been granted on naturally occurring chemicals.

Specifically on the subject of genetic patents, a joint statement of the USPTO, EPO and JPO[1] confirmed that genes were patentable. More recently the new European Biotechnology Directive[2] and the EPO Examination Guidelines also confirmed this.

Gene libraries

While there are no general objections to cloned genes being novel, as required by the European Patent Convention (EPC),[3] more specific questions should be asked. For instance, would a gene be held not novel because someone had already cloned it and it was contained in a DNA library?[4] In *Biogen*[5] it was held that the proper criterion was whether the gene was available to the public. Contained in a library, lost among thousands of other genes, it was not more available than lost within a chromosome in a cell.

The next question is whether the patent would be anticipated if a scientist had sequenced the gene as part of a routine or mass sequencing (such as the Human Genome Project). In such a case he would not yet have assigned a function to this sequence. It would not carry a technical teaching as no one would have worked out what to do with it. No invention would be enabled or in fact even envisaged at this stage.

Only enabled technical teachings can be taken into account in assessing the state of the art and novelty.[6] To be novelty-destroying, a technical teaching must be "firm and unambiguous"[7] and must *directly* lead to what it purports to anticipate.[8] Clearly this is a high threshold and mere sequence information will not suffice.

It is therefore unlikely that the previous sequencing of any gene (undistinguished from others or as part of a mass screening or sequencing project) would prevent a finding of novelty in respect of an invention based on such gene.

The Trilateral Projects

These previous cases involved the novelty of an isolated gene against a state of the art made of a multitude of genes un-isolated from each others. These did not address the situation where a gene was isolated and could be anticipated by another specifically isolated fragment, similar in sequence or overlapping with it. While there is little conclusive case law, these problems were

---

[1] Reported in 1998, 7 Biotechnology Law Review 159 to 193.
[2] Art 3.2 Directive 98/44 on the legal protection of biotechnological inventions.
[3] Art 54 EPC.
[4] Such libraries are bacterial cultures containing fragments of DNA; what sequences are present is often not even known.
[5] T301/87.
[6] T158/91 and T206/83.
[7] T479/97.
[8] T400/99.

considered by the joint Trilateral Project 24.1 between the EPO, USPTO and JPO.[9]

The EPO, USPTO and JPO stated that if the full coding sequence for a gene is known (presumably even with a full technical teaching) then a fragment of such a gene would be novel.[10] It can be extrapolated that the reverse is also true as a full sequence contains added subject-matter over a fragment and thus cannot be anticipated by it.

Similarly, sequences differing only from one another by an allelic variation[11] or the degeneracy of the genetic code will not anticipate each other.[12] Finally, a gene cloned in a species will not anticipate a homologue in a different species.[13]

It follows from the position of the three main patent offices that a clone of genomic DNA is unlikely to anticipate a clone of cDNA (or the reverse) as their respective sequences are different and it is difficult or impossible to extrapolate the sequence of one from the other. Similarly, a cDNA would not anticipate the protein it codes for (or the reverse) as they are different biochemical products and their respective sequences cannot be reliably extrapolated from one another.

In conclusion, it appears that only full sequence identity between two cloned and sequenced genes can result in anticipation of one by the other.[14]

Invention versus Discovery and the Requirement for Utility

It is a requirement of patentability that an invention has industrial applicability or utility.[15] This requirement has not posed fundamental problems until the rise of biotechnological inventions. While, classically, a discovery is not patentable[16] but an associated invention can be, the distinction becomes blurred in the field of biotechnology.

The new Biotechnology Directive[17] elaborates on the subjects of function and utility and their implications for the difference between discoveries and inventions. Unfortunately a careful examination reveals certain contradictions, discussed below.

Article 5.1 of the Directive states that the discovery of an element of the human body, including a gene or a fragment thereof, is not patentable. Notwithstanding the above, Article 5.2 provides that when isolated from the human body by means of a technical process the very same sequences can be patentable, presumably because they would now be inventions.

This distinction ignores the fact that all genes that are discovered have to be isolated first, by various technical methods. This is because genes exist within cells in chromosomes. In order to discover them, a scientist must first separate them, replicate them and finally isolate them. The same applies to cell cultures. Therefore the prohibition in Article 5.1 is incompatible with Article 5.2 and ineffective.

The distinction between invention and discovery in the Directive must thus be found elsewhere. Recitals 20 and 22 provide an alternative explanation. Recital 20 adds to the requirement of technical isolation the further requirement that the isolate be susceptible of industrial application. Recital 22 further requires that such application be disclosed in the patent application. This suggests that it is the industrial application which converts the discovery into an invention, a view shared by other practitioners.[18]

"Industrial application" is not defined in the Directive, but presumably relies on the established case law and the EPC. The EPC requires that a patentable invention be capable of being made or used in industry.[19] The UK Act which implemented the EPC uses an identical wording.[20] However, many contradictions have arisen with the word "made" as any known compound can be made by industrial means and especially DNA, whether or not it has any usefulness. This problem of interpretation is acknowledged by the EPO[21] and by practitioners[22] alike.

At least in UK national law, the correct interpretation was stated by the Court of Appeal in *Chiron Corp v Murex Diagnostics Ltd*,[23] where it was held that "made in industry" meant for the purposes of industry, so that a useless DNA fragment could be made *by* industry but would never be made *in* industry. Such a precedent is, however, not binding on the EPO.

It is submitted that the Biotechnology Directive does solve this problem (at least for biotechnological inventions) as Article 5.3 clearly refers to industrial application while other recitals require indication of function, technical information and again industrial application.[24] No scope is left for inventions which have no utility but which can be manufactured albeit for no purpose.

---

[9] Trilateral Project 24.1: Biotechnology comparative study on biotechnology patent practices. The full text can be found at www.epo.co.at.

[10] *Ibid* at 2.2; this point was also confirmed in T886/91 in relation to overlapping sequences.

[11] A naturally occurring variation in a genetic sequence.

[12] Trilateral Project 24.1 at 2.2.

[13] *Ibid*.

[14] Although there is no EPO ruling exactly to this effect, the reasoning of the Board in T1095/00 and T886/91 is fully consistent with this assertion.

[15] Art 57 EPC.

[16] Art 52(2)(a) EPC.

[17] Directive 98/44 on the legal protection of biotechnological inventions, which is incorporated into the EPC by Rule 23b(1) EPC.

[18] *Patenting (partial) gene sequences taking particular account of the EST issue*, IIC Vol 30 No 1 1999 p 1, Andreas Oser.

[19] Art 57 EPC.

[20] s 4(1) Patents Act 1977.

[21] Trilateral Project B3b: Comparative study on biotechnology patent practices; Theme: Patentability of DNA fragments. The full text can be found at www.epo.co.at.

[22] Andreas Oser, *supra*; *The EPO's position: the patentability of genomics-based inventions*, Patent World, October 2001 p 30, Dr. Siobhán Yeats.

[23] [1996] RPC 535.

[24] Recitals 22, 23 and 24 *supra.*

There is yet a further source of confusion in the meaning of the function or the utility of a gene or the protein(s) it codes for. With the advent of bioinformatics it has been possible to obtain a rough guess of the type of protein that a gene codes for. As a result, many have claimed to know the "function of a gene" through computer modelling.

Often technical effects (or industrial applicability) and the endogenous function or activity of a protein or a gene are referred to indistinctly. But how is that putative function in the organism related to the industrial applicability required under patent law? Again, different parts of the Directive seem to offer different insights. Recital 24 appears to refer to the function of the protein within the organism.[25] However, Article 5.3 refers to the *industrial* application of the protein. Recital 23 uses the word "function" on its own and thus can be interpreted both ways.

The endogenous function of a protein is likely to be related to its industrial (or rather medical) application but the former is a supposition or a hypothesis while the latter is a concrete and useful application. In addition, what bioinformatics provides is an idea of the class of protein to which the gene belongs. Its actual use by the organism is still a different matter and its elucidation can involve years of research. In such circumstances, the actual technical application is even more remote.

It is debatable how much information on the industrial application of an invention is required under the EPC[26] but the Directive adds to the normal rules an additional requirement to provide a minimum set of information on the nature and endogenous function of the protein and expressly and convincingly to disclose the said industrial application. This would have been intended by the legislature as a means of stemming the flow of claims involving thousands of gene fragments, especially as the definition of utility could include the useless (provided that it could be manufactured).

It must also be noted that some parts of the Biotechnology Directive specifically refer to human genes while others do not, thus raising the possibility of divergent legal requirements for the patentability of human and non-human DNA sequences notably for the disclosure of their technical application.[27]

The Trilateral Projects have provided more detailed examples of the requirement for utility as homology data can be used to relate new sequences to old ones for which some information exists. These were considered by the EPO, JPO and USPTO for both full-length sequences coding for proteins and for gene fragments, useful only as probes. In both cases the utility was inferred from homology to known sequences. These are considered below.

[25] "which protein [...] is produced or what function it [the protein] performs".

[26] *The patentability of Genome Project derived DNA inventions in the EPO*, Patent World, August 2001 p 30, H.R. Jaenichen, F. Stolzenburg and A. Dick.

[27] Arts 5.1, 5.2 and 5.3 Biotechnology Directive *supra*.

Utility inferred on homology for coding sequences

The EPO requires a utility that is plausible[28] or credible beyond mere speculation.[29] In addition, the EPO requires "specific utility".[30] This is not defined but is identical to the USPTO definition of utility ("specific and credible"). For the USPTO, the word "specific" is meant to prevent a general utility that a multitude of similar compounds have.[31]

Specifically, the EPO will not accept homology data if the homology is below 55% or if it involves only homology across a protein motif.[32] However 80% homology in the DNA sequence (and 95% at the protein level) could be acceptable if across the whole coding sequence and not a restricted region (or motif).[33] In addition, the EPO reserves the right to ask for more experimental data if the homology does not appear sufficiently convincing.

In all the examples considered within the Trilateral Projects, the utility of the homologous protein is deemed established. If the homologous protein has itself no utility then the new sequences cannot have any.

However, it is possible to construct a general utility for any gene sequence X by stating that X is used to treat or diagnose a disease in which gene X is involved (by mutation, deletion or otherwise). The EPO makes no comments as to such claims. The USPTO on the other hand positively responds that such use has no specific utility.[34] As the EPO also requires "specific utility", it can be assumed that the EPO also would find such claims non-specific in respect of utility.[35]

Utility inferred on homology for gene fragments (ESTs)

Gene fragments can be used mostly as tools to obtain the full-length gene (the target gene, whether in the same species or in a different one) and as probes to ascertain the expression level of genes. They cannot be used to make the protein which is associated with the gene.

The EPO takes the view that where the target gene has no specific utility or is not distinguishable from others then

[28] Trilateral Project 24.1 at 2.1 *supra*.

[29] Trilateral Project B3b: Comparative study on biotechnology patent practices; Theme: Nucleic acid molecule-related inventions whose functions are inferred based on homology search. The full text can be found at www.epo.co.at.

[30] *Ibid*.

[31] The example used by the USPTO is a transgenic mouse being useful as snake food, a utility shared by all mice.

[32] i.e. a restricted region albeit important or significant in terms of function.

[33] Trilateral Project B3b on homology, cases 9 and 10, *supra*.

[34] *Ibid* cases 3 and 6.

[35] This is supported by the recent EPO case T241/95 which confirmed that a patent application had to disclose a "defined real treatment" of an illness for a therapeutic utility to be established.

such fragments have no *specific* utility.[36] However, if the fragment acquires a specific utility by enabling the diagnosis of a known disease (by being used as a probe), then it will have industrial applicability under the EPC.[37]

Presumably, if the EST enabled the obtainment of a target sequence which had specific utility then the EST would itself have specific utility.[38]

Unity

It is a requirement of the EPC that the subject-matter claimed in a patent has unity,[39] meaning that the claimed inventions must share a single inventive concept.

The case law of the EPO has further stated that only inventions which had a common technical feature that contributed to solving the technical problem which formed the basis of the invention, had unity.[40]

As a result this common technical feature had to be inventive[41] (although this requirement is only to the point of contributing to the inventiveness and not to be sufficient to be patentable in its own right[42]). This is determined by using the problem and solution approach which is used to assess the inventive step.[43] It follows that this common feature cannot be part of the state of the art[44] (otherwise it could not be inventive).

In addition, unity is not concerned with structure.[45] Sequence homology would therefore not *per se* result in unity (in contrast, the USPTO would find no unity where there is no homology[46]). Only the technical application will be considered by the EPO.

Therefore to label a group of sequences as being receptors or transcription factors (or as belonging to any general class of proteins) because of homology to known genes will not be sufficient to provide unity of inventive concept. However, this can be overcome if they belong to a class of proteins which have previously unknown properties (so as to be inventive).

This is confirmed in Trilateral Project B3b on DNA fragments where the EPO stated that a multitude of cDNAs have no unity as such (even if obtained from the same biological source), while a set of them enabling one to diagnose a specific disease has.[47] The unifying concept would be the diagnosis of a disease.

This position of the EPO can cause problems for the patentee of a gene. Suppose that the gene is claimed and so are alleles, variations and mutations of it. The sequence similarities will be disregarded. If the uses of the normal and the mutant gene are different because the mutant is non-functional, then there would be no unity. It is clearly very easy to include in the claim, sequences which have no unity.

Enablement and Clarity

Article 83 of the EPC provides that a European patent application must disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art (enablement). This is further supplemented by Article 84 which requires clarity of the claims. Although these are distinct legal requirements, in practice difficulties with these arise together.

To define and enable the uses of conventional inventions can be difficult anyway but, with DNA, the variability of sequences, the poor reproducibility of molecular techniques and the plurality of the functions of proteins create new problems. As enablement is a potent regulator of the scope of patent protection, it is an important requirement to consider. The case law is extensive but this writer will concentrate on the principles which are most relevant to biotechnology.

Firstly, the disclosure must enable the invention to be workable across the whole range of the products claimed.[48] This is clearly an onerous requirement. The disclosed invention must further be reproducible without undue burden[49] or the use of inventive skills.[50] What precisely constitutes "undue burden" is unclear. Having to proceed by trial and error would constitute undue burden[51] but a "difficult, complex and time consuming" procedure to clone a gene would not.[52] Finally, identifying a ligand for a known receptor without structural information on the ligand would be an undue burden.[53]

More specifically, for biotechnological inventions the real problem can be reproducibility; and if a general principle is claimed, whether the invention is workable in an area where it has not been tested.

The EPO has made allowances for variability in biotechnology and an invention will be enabled even if there is some variability in the starting material, as long as one can obtain members of the class claimed.[54]

---

[36] Trilateral Project B3b on DNA fragments, *supra*. Assuming that there is no utility merely because the sequence can be "made *by* industry".
[37] *Ibid* cases D and E.
[38] *Ibid* cases B and F; this was not expressly discussed by the EPO but by the USPTO.
[39] Rule 30 EPC.
[40] W11/89.
[41] W6/90.
[42] W45/92.
[43] W10/92. See below for a discussion of the problem and solution approach.
[44] W9/93.
[45] W48/90 and W50/90.
[46] Trilateral Project B3b on DNA fragments, cases G, H and I, *supra*.
[47] *Ibid*.

[48] T409/91 "within the whole area […] claimed" and T435/91 "substantially all embodiments of a claimed invention [...] can be put into practice".
[49] T226/85.
[50] T931/91.
[51] T32/85.
[52] T223/92.
[53] Trilateral Project B3b: Comparative study on "reach-through claims". The full text can be found at www.epo.co.at.
[54] T301/87: this decision also states that an invention is sufficiently disclosed if *one* way of performing the invention is disclosed, however this was reinterpreted in T435/91 as consistent with the requirement of being workable *across the whole range* of the claim.

As to whether an invention is workable across the whole range claimed, it will take serious doubts and verifiable facts to the effect that the invention will not work, to justify a finding of lack of enablement.[55] This is a question of fact or rather of how convincing the preliminary experimental data are. This has resulted in diverse findings. In T187/93, a general principle of immunoprotection by preparing antibodies against a virus was held not sufficient for the patent to cover any viruses but was upheld if restricted to the herpes viruses, on which experiments had been performed. A patent on mice carrying an oncogene was held to cover the extension to other mammals[56] while the genetic modification of a plant was held not to be extendable to other plants.[57]

A further problem for DNA-based inventions is that by using a definition for the claimed class which encompasses variations or deemed equivalents, one is likely to claim more than is enabled. This is addressed by the Trilateral Projects and some case law of the EPO discussed below.

In the *Human Tissue Plasminogen Activator (t-PA)* case,[58] the original patent claimed a protein which had "tissue plasminogen activator function" and which corresponded to a protein sequence either identically or through an unspecified number of substitutions, insertions or deletions of amino acids.[59] The patent was opposed and the Board held that the claims were unclear and encompassed potentially more proteins than were enabled. The patent survived in an amended form where the functional definition was supplemented by a biochemical test for the plasminogen activator function, fibrin binding properties and immunological properties of the said protein. This was held sufficiently clear (within the requirements of Article 84 EPC) and encompassed only proteins in respect of which there was sufficiency of disclosure (to comply with Article 83 EPC).

The Trilateral Projects have developed this area by focusing on general examples discussed below.

In Trilateral Project 24.1, the EPO stated that a claim to a sequence defined by having the function of an endogenous protein would not be clear (because proteins can have many different functions) or enabled (as in the *t-PA* case). A claim to sequences defined as having 40% homology to a disclosed sequence would not be clear either, as the homology is too low to ensure that the products would be even similar,[60] but would be enabled. Similarly, a claim defined by addition, substitution or deletion from a disclosed sequence would not be clear unless the functions or properties of the products are defined and the substituted sequences have high homology to the original one (to maintain overall homology). However such a claim would be enabled as such because the sequences can be made. Finally, where a claim is specified as encompassing allelic variations and equivalent mutations, the EPO would require that these be restricted to sequences having the same specified functions in order to be clear but would be enabled as such (again because they can be made).

The EPO's position within Trilateral Project 24.1, that a compound is enabled because it can be manufactured, is expressly restated in Trilateral Project B3b on the patentability of DNA fragments but is contradicted in Trilateral Project B3b on homology. This is also in contradiction with the EPO case law as an invention must be disclosed so as to be workable in its entirety (and not merely in order to obtain the starting material).

Only the USPTO and the JPO made the point in relation to enablement that such open-ended definitions encompass a multitude of sequences which are unlikely to all have the desired properties and thus cannot be enabled. A significant number (or even most) of the sequences which fall under the claim because of the wide definition are not part of the invention.

In addition, the EPO stated that there was no difference between a claim to a given sequence and a claim to any sequence comprising the given sequence.[61] This disregards the fact that the latter comprises an infinite number of sequences of any length (and could even apply to whole chromosomes), which cannot all be enabled (as pointed out by the JPO).

This appears anomalous. However under Article 69(1) EPC the description can be used to interpret the claim and its scope so as to avoid a finding of insufficiency.[62] This has led the EPO in Trilateral Project B3b to state that a claim to DNA fragments comprising a given sequence was restricted to the sequences that were usable for the claimed invention.[63] As a result, all the claims that were not enabled (or which did not have unity of concept) were implicitly excluded. With such construction, the problems with sufficiency of multiple sequences can be overcome. However Article 69(1) probably only applies to Article 83 and thus affects only enablement but not clarity.[64] This may explain the marked difference between the requirements for clarity and sufficiency as stated in the Trilateral Projects.

In spite of the conclusions of the Trilateral Projects, when patenting a DNA invention defined through homology to a disclosed sequence or as an allele thereof (whether natural or engineered), to avoid a finding of insufficiency and lack of clarity, it may be necessary explicitly to restrict the claim to the variants or alleles which have the desired property. Such property must be ascertainable by an easily reproducible test so that one could know easily whether one is operating within the area claimed.[65]

[55] T19/90.
[56] T19/90: see T386/94 for a similar result in bacteria.
[57] T612/92.
[58] T923/92.
[59] In fact any protein can have homology to any other one through an unspecified number of amino acid substitutions, insertions or deletions.
[60] The response of the EPO to this question suggests that if the homology was higher then such a claim could be clear.
[61] In the Trilateral Project B3b on DNA fragments.
[62] T238/88.
[63] In the Trilateral Project B3b on DNA fragments, case E *supra*.
[64] Under T454/89, T760/90 and T2/80 the description cannot be used to remedy a lack of clarity or a logical defect in the claim. However, T860/93 states the opposite, provided that the claims are not logically defective.
[65] T256/87 and T923/92 which apply to both Arts 83 and 84 EPC.

Inventiveness

The problem and solution approach

The requirement for an inventive step is the most central of patent law. Article 56 EPC provides that, having regard to the state of the art, the invention must not be obvious to a person skilled in the art.

There is much case law and legal writing on this subject, but, for the purposes of this publication, only the aspects of inventiveness which are specifically problematic for DNA-based inventions will be discussed.

In order to assess inventiveness, the EPO is using the problem and solution approach which was developed through case law.[66] The *Triazole* case[67] states the workings of this approach comprehensively. Firstly, one must objectively assess the technical results achieved by the claimed subject-matter, compared with the results obtained according to the state of the art. Secondly, one assumes that the inventor in fact did try to achieve this result. This assumption is used as a basis from which to define the technical problem to solve. Thirdly, one must determine whether, for a skilled but unimaginative worker, it would have been obvious to solve the technical problems and achieve the result.

Additional cases have explained this test further. In T2/83 it was held that the test was not whether the worker could arrive at the solution by chance but rather, whether he *would* find it if confronted with the technical problem. If there was no reasonable expectation of success in a given technical approach, the skilled worker would avoid it. In the *Biogen* case,[68] the term "reasonable expectation of success" was clarified as being distinct from the hope of succeeding. For an inventive step to be denied, it must be shown that the skilled worker would reasonably predict at the outset that he would be successful, not that he hoped that he would.

In the genetic engineering case *Unilever*,[69] it was held that for molecular biology there will be no inventive step if the work to solve the technical problem is straightforward, notwithstanding that it may involve considerable work.

In summary, if the notional worker would not have been able to make the step from prior art to the invention because he could not or would not then there is deemed to have been an inventive step.

One noticeable result of the problem and solution approach is that if a new product shows an unexpected or surprising effect (judged with reference to the state of the art), then it will be inventive because the new effect is deemed to have been the goal of the research. The notional worker would be deemed to have tried to achieve this effect and as it is not part of the state of the art and not obvious (as it is unexpected), he would fail.[70]

Structural originality is not taken into account when assessing inventiveness.[71] Therefore, when a group of compounds fail to have any specific technical application there is no technical achievement and the problem to be solved is deemed to be the provision of further variants which in the absence of a technical motivation for doing so is obvious.[72]

Inventive discoveries

In molecular biology often an invention results from a discovery (which on its own is not patentable) combined with the technical use of the discovery (which may be self-evident once the discovery is made).

As a result, most of the inventive work could be performed during the research phase. It has been suggested that inventiveness in the discovery process is merely an indication of overall inventiveness.[73] However it is submitted that under the problem and solution approach, the technical problem can be any step between the state of the art and the invention. It is irrelevant whether it is a new compound, or its technical effects or a process to obtain it or overcoming a difficulty in obtaining it. The only factor is whether the notional skilled worker would have been able to obtain the result without inventive activity.

Hence, the technical problem can be the part of the invention which could be labelled "discovery". The fact that the technical use is obvious once the discovery is made should not be an objection to inventiveness. It is submitted that conclusive proof of an inventive step can be provided from any stage of the obtainment of the claimed subject-matter.

There are nevertheless differences in the requirements for an inventive step to be present, depending on whether it is found in the obtainment process or the technical effect. These are specifically relevant to genetic inventions and are discussed below.

Firstly, if there is no inventive step in the obtainment (or isolation or discovery) of the product but it has a technical effect: then provided that the technical effect was not reasonably expected or predictable from the state of the art, there is a deemed inventive step.[74]

Secondly, assume that an inventive step was taken during the obtainment, but the result does not show any surprising or distinguishing features. This problem is now more complex. The *Triazole* case is often used to hold

[66] T20/81 and T1/80, among many.
[67] T939/92.
[68] T296/93.
[69] T386/94.

[70] However, if the effect is merely a "bonus effect", being an improvement that was expected (even if an extra unforeseen effect was in fact obtained) then the technical achievement will still be obvious. See T226/88.
[71] See T22/82 and T111/00 specifically for DNA sequences (unlike in the USA, where under *Re Deuel* 51 F.3d 1552 (Fed. Cir. 1995), sequence originality is now conclusive proof of an inventive step).
[72] *Triazole*, T939/92.
[73] Andreas Oser, *supra*.
[74] See Trilateral Projects 24.1 and B3b on DNA fragments, *supra*.

that a group of chemicals without a specific function cannot be inventive because they consist of the obvious provision of further variants.[75] However in the *Triazole* case there was no argument put forward to the effect that the synthesis of these compounds was anything but straightforward. In addition, it was assumed that the compounds had no function whatsoever. It is submitted that this precedent cannot apply exactly to this situation. However, starting from first principles, under the problem and solution approach if there is no technical utility (or a specific one) there can be no inventiveness as there is nothing for the notional worker to aim for. There is no technical improvement over the prior art and thus no problem to solve. If there is, however, some specific technical use (no matter how simple) the test reduces to determining whether the said worker could have taken the steps to obtain the product. If this involved an inventive step to overcome some difficulties, then there will be deemed to have been an inventive step.[76] It would appear that if the obtainment of DNA sequences required an inventive step and even a simple, but specific, utility was disclosed, then these could be found inventive. Such finding could have far-reaching implications for mass cloning endeavours such as the Human Genome Project.

The Trilateral Projects

The Trilateral Projects further extend these notions by giving precise general examples of inventiveness or lack of it.

The Trilateral Project B3b on DNA fragments confirms that a group of sequences with no specific utility cannot be inventive. It is further stated that cloning random DNA sequences is never inventive (as it is routine and has no specific utility). All ESTs are thus obvious (provided that they have no specific utility).

However, in agreement with the problem and solution approach, if a gene fragment can be used to diagnose a specific disease then it would have specific utility and would be inventive as it has an unexpected effect.[77]

In Trilateral Projects 24.1 and B3b on homology, the EPO regards the obtainment of a new allele of a gene or a new family member as obvious as it involves routine techniques. This is in agreement with the JPO but not the USPTO which, using the *Re Deuel*[78] principle, easily finds inventiveness on the ground of sequence originality.

The EPO's position is very clear cut. However cloning gene homologues in the same species or cross-species can be more difficult than it appears. Apart from the fact that it can be very difficult to clone a given gene, there is no guarantee that a corresponding gene exists in different species. Any expectation of success could be ill founded. It is submitted that it is not possible to have such an absolute stance and that each case should be judged in the light of the available evidence, the actual difficulty and the expectations of a skilled worker embarking on the cloning exercise.

Conclusion

In summary, there can be an inventive step, either if the processes necessary to obtain a DNA sequence were inventive and the products have specific utility; or if the said sequence exhibits a surprising effect not expected from the state of the art.

As now most cloning is deemed to be routine, in the absence of unexpected effects, such subject-matter would normally be deemed obvious.

In addition, the reader's attention is drawn to the fact that in the *Triazole* case it was stated that a group of compounds cannot be inventive if not *substantially all* of them are inventive. This causes problems similar to those for unity and enablement, when a group of sequences is claimed. In the absence of a functional definition supplementing the structural one, there is a substantial risk that some members of the claimed class will have no specific utility and will be obvious under the *Triazole* principle, as well as failing the unity and enablement tests. Again, the solution could be drafting to exclude all variants that are not useful and the fact that the EPO may construe the claim so as to exclude variants with no specific utility. However, it is unclear to what extent the description can be used under Article 69(1) EPC to restrict a claim which is excessively broad.[79]

Patentability of Various DNA Classes: The Extent of Allowable Claims

Because the various requirements for patentability are considered separately in law, this may result in a fragmented vision of the field. A single failed legal test in respect of inventiveness, novelty, clarity, technical applicability or sufficiency will be fatal to a patent. It is therefore necessary to consider all aspects of patentability at the same time in respect of different broad classes of DNA inventions. These are considered in turn below.

Single discrete class genetic inventions

These are inventions in respect of a single DNA sequence, without any claim to variations, homologues or derivatives.

[75] See the Trilateral Project B3b on DNA fragments, *supra*.
[76] See T343/98 for a recent confirmation of this point.
[77] Trilateral Project B3b on DNA fragments, cases E and D, *supra*.
[78] *Supra*.

[79] T607/93 states that the description cannot be used to restrict an excessively broad claim when assessing inventiveness and novelty while T327/87 and T238/88 are interpreted as stating that the description can be used to determine the subject-matter of the patent and its scope.

Single coding sequences

This will be a patent in respect of the coding sequence of a gene. Typically, it will involve cDNA obtained by reverse transcription, will lack any intron sequences and can be used to manufacture the protein it codes for.

Such a sequence will not be anticipated by its existence as an un-isolated sequence in a bacterial library or a sequence database. Nor will it be anticipated by a similar but different sequence that was previously isolated.

In the absence of an unknown or unexpected effect (judged with reference to the state of the art), this will be held obvious. Under the terms of the Biotechnology Directive, the function of the protein must be disclosed together with its industrial use in the patent application.

Expressed sequence fragments

These have been termed ESTs and are incomplete fragments of a coding sequence. Their only utility could be either as probes to obtain the full-length sequence or to measure the expression level of a gene. For the latter, its only specific utility is to diagnose a disease or a genetic configuration.

Such a fragment will be novel even over the full-length sequence from which it was isolated. Unless it has a specific utility,[80] it will not be held to be inventive and patentable. However, a distinguishing effect, such as being used as a probe to diagnose a precise disease, would reverse this finding.

The requirement in the Biotechnology Directive to disclose the function of the protein (Recital 24) does not apply to such a fragment as it would not be used to produce a protein. However, arguably, Recital 24 is a specific example of the requirement of Article 5.3 given for the avoidance of doubt and there is in fact no lesser requirement in respect of un-translated sequences. (Therefore the industrial use of the sequence must be disclosed.)

Genomic regulatory sequences

These are fragments of genomic DNA and more particularly of the regulatory sequences thereof (promoter sequences). These are very important in regulating gene expression and can be used for a variety of genetic engineering uses. They are shorter in length than coding sequences and *any* variation in sequence is likely to modify their function.

The Trilateral Projects did not consider such regulatory sequences as they concentrated on full or partial coding sequences. Such sequences are non-coding and thus Recital 24 of the Biotechnology Directive does not apply to them. For these to be inventive and have a specific utility, a patentee will be required to disclose what industrial (or medical) function the sequences can be made to perform. Simply to state that a sequence can regulate gene expression will not be sufficient. On its own, such a promoter region is unlikely to be patentable unless it exhibits an unexpected effect. Such effect could be, for example, to be responsive to certain environmental factors (such as temperature) or to be able spontaneously and randomly to activate with low frequency (a useful feature for marking clonal cells).

Multiple class genetic inventions

Often, claims to DNA inventions will attempt to extend to modified versions of the cloned DNA. The problems with their patentability are the same as with the above, but in addition, they risk claiming more than is justified by their contribution to the art, because of their open-ended definitions. These are discussed and grouped below according to the method used to define their scope.

Defined by homology to a given sequence

This was used in the *Chiron NANBV* case.[81] This definition, on its own, encompasses a large number of DNA sequences. In order not to fail for lack of enablement, inventiveness and unity, the patent application must be able to convince an examiner that substantially all the claimed sequences have the function required for the invention. With a 40% threshold this is doubtful as a single variation can disrupt the working of a DNA sequence (by introducing a stop codon, for instance). In addition, the smaller the reference sequence, the easier it is to match it with a given homology to unrelated sequences. (The reader's attention is drawn to the fact that our own genome is at least 70% homologous to that of frogs.)

This is recognised by the EPO in respect of the requirement of clarity. This problem may be solved by restricting the claim further, to the sequences which exhibit a special activity, well defined and easily ascertainable. In addition, the EPO may implicitly restrict the scope of the claim under Article 69(1) to only the enabled sequences.

Defined by sequence variations or reference to alleles

The EPO holds that it is now routine to produce substitution or deletion variants from any cloned gene and that cloning an allele of a gene using a different allele is also a routine practice. In that respect a patent claiming such derivatives is enabled. However, it is open to the same criticism as described above in respect of the confidence in the fact that all members of the claimed class possess the requisite properties and functions. As there is an almost infinite number of sequences that can be generated by substitution or deletion, they must be at least confined to high homology variants which still possess the original function.[82] It is possible, for instance, with certainty to claim all variants of a coding sequence

[80] Which cannot be simply, that it hybridises to other homologous sequences or that it can be used as a general screening tool.

[81] T188/97.

[82] Trilateral Project 24.1 *supra*.

which produce a given protein (there is more than one because the genetic code is degenerate and one can predict all the sequences that will result in exactly the same protein). Regarding alleles (which are naturally occurring substitution or deletion variations) the patentee may unknowingly include non-functional variants. If they are not claimed as such, they may be excluded from the protection of the patent. Nevertheless, far from being useless, these would be the disease-causing alleles and thus are at least as important as the normal ones.

Defined by being part of a family of proteins or being a homologue in a different species

The problems are very similar to claims defined by reference to sequence variations or alleles but the very existence, characteristics, structure and functions of the claimed additional subject-matter is even less certain. It is therefore very doubtful whether such claims ought to be allowed at all.

The American case *Eli Lilly*[83] held that a patent claiming the rat cDNA for insulin would not extend to the human coding sequence. Although the EPO considers that cloning a homologue in a different species is usually routine work (and thus is enabled), it does not follow that claims ought to be extended across species (or even to other gene family members within the same species). It is submitted that if indeed it is so easy to obtain these sequences, then the patentee could reasonably be required to have done so before claiming them.

Defined by a functional test

These can claim all DNA sequences whose corresponding proteins satisfy a biochemical test or have a particular function. The latter is precisely the approach that failed in the *t-PA* case, T923/92. The main problem is lack of certainty, which in turn will cause difficulties under sufficiency (Article 83 EPC) and clarity (Article 84 EPC). In addition, if the exact members of the class cannot be ascertained then it is unlikely that there will not be real doubts as to whether all members are enabled.

In the *t-PA* case the functional test which was allowed had to include the ability to catalyse a reaction, bind to a known compound, in addition to structural data in the form of a DNA sequence and the binding to antibodies raised to recognise the structural conformation of the t-PA protein.

It must be noted that if the claimed sequences are defined by reference to a function it may not be possible for the EPO implicitly to restrict the claim to the useful sequences under Article 69(1) because the claim may be deemed unclear and would fall foul of Article 84.

Claims to full-length sequences from partial ones

This involves a DNA fragment being patented and an express claim made to all sequences incorporating it or to the full-length coding sequence or gene. This can arise by claiming sequences "comprising" the patented sequence. As for other wide claims discussed previously, an open construction would include an indeterminate number of sequences of any size and ought to fail for lack of sufficiency, unity and inventiveness. Again, the EPO may construe such a claim as being limited to the sequences useful for the patented invention. In addition, this claim could be interpreted as claiming the results of further research and thus as a "reach-through" claim which is likely to fail (see below).

"Reach-through" claims

Such claims go further than those described previously and attempt to claim products derived through further research from the subject-matter of the patent and even the uses of these. In the context of molecular biology this may involve claiming all the ligands of a cloned receptor or all the binding partners of a protein or all compounds isolated using the patented sequence. The numbers of such claims are sufficient to have justified a new Trilateral Project devoted exclusively to them.[84]

The Trilateral study is detailed but the main principle that clearly emerges is that compounds that are claimed through a "reach-through" claim will have to be structurally defined. Therefore only those that are already isolated and characterised by the patentee can be claimed. Thus, the requirements for patentability appear to be identical to those arising, had the additional compounds been claimed on their own. It is not clear from the study whether special allowances will be made regarding the inventiveness of the claimed invention (so that the inventiveness of the receptor could be used for the assessment of the inventiveness of the ligand) and whether the combined claim lacks unity, as it claims compounds whose only technical relationship is that they bind to each other (or that they belong to the same physiological pathway).

Infringement and Protection of Patent Rights

The situation where DNA sequences are expressly claimed is dealt with in the previous section. In this one, the question that will be addressed is whether a patent can, by virtue of infringement laws, implicitly protect sequences other than the ones *expressly* claimed.

[83] *Regents of the University of California v Eli Lilly & Co* 119 F.3d 1559 (Fed. Cir. 1997).

[84] The Trilateral Project B3b: Comparative study on "reach-through claims", *supra*.

The scope of protection granted by a patent is decided under the terms of the EPC. Notwithstanding this, infringement is judged solely by national law.[85]

As a result, two separate questions must be asked in respect of a potential infringement: firstly, does the patent protect the subject-matter and, secondly, is there an infringement in national law? Both these questions must be answered in the affirmative for an infringement to occur. Consequently, in order to discuss this matter exhaustively, one should refer to the national provisions of all EPC member states. This is an unsatisfactory situation. However, there are similarities in national patent protection regimes (as a result of either convergence or the Biotechnology Directive) and some general principles can be delineated.

Products, processes and products thereof

Firstly, under UK law there is a distinction between product and process patents. An infringing action in relation to a product patent can be to manufacture it.[86] For a process patent it would be, *inter alia,* to use the process or to supply any product directly obtained from the said process.[87]

The meaning of "product directly obtained" was held under UK law in the *Pioneer* cases to exclude any products obtained through additional intermediate steps.[88] A product protected as the direct product of a patented process would lose this protection if it lost its identity and essential characteristics through further processing.[89] This ruling involved compact disks and their method of manufacture from a master disk. While the subject-matter is very different from DNA, a clear parallel can be drawn as genomic DNA is the template from which messenger RNA is made and which itself contains the information for protein translation. In the *Pioneer* cases, the three steps from master disk to finished CD and the fact that the master disk could not be played on a CD player were held to make the production indirect and the essential characteristics of the master disk lost. Therefore the numerous stages of DNA processing and the different properties of the various intermediates would result in a finding that a process patent using a DNA sequence will not protect a protein derived from it, or possibly even mRNA transcribed from it.

The Biotechnology Directive I

The Biotechnology Directive which must be implemented by the European member states in their own national law (therefore relevant to infringement in national law) has modified the legal tests for infringement in relation to DNA.

The Directive states that a product patent on biological material: "shall extend to any biological material derived from that biological material through propagation or multiplication in an identical or divergent form and possessing those same characteristics [of the protected biological material]"[90]; and a patent on a process enabling a biological material to be produced "shall extend to biological material directly obtained through that process and to any other biological material derived from the directly obtained biological material through propagation or multiplication in an identical or divergent form and possessing those same characteristics [of the biological material produced by the patented process]".[91]

In addition, the Biotechnology Directive requires that the protection of a patented product "containing or consisting of genetic information shall extend to all material […] in which the product is incorporated and in which the genetic information is contained and performs its function".[92]

The implementing regulation in UK law merely repeats the same wording[93] without offering any further guidance and the recitals of the Biotechnology Directive do not offer any tools for interpretation. Without having precise definitions for "divergent propagation", "multiplication" or for the "function" of "genetic information" it is very difficult to interpret these articles. However some statements can be made. Firstly, these appear to go beyond the normal principle that the direct products of process patents are protected.[94] Secondly, these seem to be concerned solely with natural propagation or multiplication, which are features of living cells (or animals or plants) and of plasmids (the usual vector of man-made DNA).[95]

This would indicate that under this new regime, plasmids, transgenic cells, animals and plants are protected by virtue of a patent on the genes incorporated in them.

Whether a patent on genomic DNA would protect the produced mRNA and the resultant protein would depend on whether DNA transcription and translation is viewed as propagation or multiplication or the incorporation of genetic information. It is not possible at this stage to offer any credible opinion and one can only hope that the EU will issue guidelines in the near future.

The doctrine of equivalents

This doctrine provides that there will be an infringement of a patent if, on a purposive construction of a claim, the

[85] Art 64(3) EPC, confirmed by G2/88.
[86] s 60(1)(a) Patents Act 1977.
[87] s 60(1)(b) and (c) Patents Act 1977.
[88] *Pioneer Electronics Capital Inc. v Warner Music Manufacturing Europe GmbH* [1995] RPC 487.
[89] *Pioneer Electronics Capital Inc. v Warner Music Manufacturing Europe GmbH* [1997] RPC 757.
[90] Art 8.1 Biotechnology Directive 98/44 *supra.*
[91] Art 8.2 Biotechnology Directive 98/44 *supra.*
[92] Art 9 Biotechnology Directive 98/44 *supra.*
[93] The Patent Regulations 2000, SI 2000 No. 2037.
[94] Because Art 8.2 restates the protection of directly obtained products and then further extends this principle to material derived from them through identical or divergent propagation or multiplication.
[95] This interpretation is supported in *UK Bites Biotech Bullet*, Patent World, November 2000 p 11, Duncan Curley.

new product (or process) is a variation of the patented product (or process) only in features that are non-essential for the invention, that such variation at the time of publication of the patent obviously has no effects and that the claim does not exclude the said variants.[96]

In relation to DNA sequences, a sequence variation between the claimed and the infringing product will prevent literal infringement.[97]

The leading case in the United Kingdom for DNA patent infringement and the doctrine of equivalents is now *Kirin v Roche*[98] and is discussed below.

Kirin (the claimant) had cloned the coding sequence (as both genomic DNA and cDNA) for erythropoeitin (Epo) and was expressing it in cell cultures to secrete and purify the protein. Its patent claimed the genomic DNA and cDNA for Epo (Claim 1) and the protein produced by the DNA sequences of claim 1 (Claim 36). TKA invented and patented a process whereby a promoter sequence could be integrated into the genome of cells close to the endogenous Epo gene and increase production of it. The secreted Epo was then purified from cell cultures. The TKA process did not use the *isolated* DNA disclosed by Kirin; rather it manipulated the natural gene *in situ* from which the Kirin DNA sequences were once derived.

The trial judge decided to consider the infringement of Claim 36 together with Claim 1, but ruled expressly only on Claim 36. His findings can be summarised as follows: 1) the Kirin and the TKA processes were equivalent as they yielded the same result and used the "same string of DNA"; and 2) TKA was helped by information disclosed in the Kirin patent to design its method. Although the Kirin patent did not constitute an enabling disclosure of the DNA used by TKA, this causal link contributed to a finding of infringement.

The following comments can be made on this decision:

It is difficult to hold that the subject-matter of Claim 1 was infringed, as it involved DNA sequences being substantially different from that of TKA which overlapped only in minor regions and radically different processes. TKA did not use *isolated* DNA for the coding sequence of Epo. To hold that Kirin's patent extends to methods which manipulate the genomic gene which codes for Epo is to hold that Kirin has a patent on the natural Epo gene in its *un-isolated* state *in vivo* which would extend to any processes proceeding through that gene.

It is submitted that this is disproportionate in the light of the technical contribution to the art and probably incompatible with the Biotechnology Directive.

Claim 36 is a claim to the product of the patented process (or product) described in Claim 1. TKA has infringed it by virtue of producing (albeit by different means) the patented product *only if* this claim is construed as extending beyond the *direct* products of the patented process. The trial judge held, in relation to infringement, that product-by-process claims extended to all products howsoever obtained, but in relation to construction that the same should be strictly construed as extending only to the direct products of the process. This contradiction has caused concern among other commentators.[99]

If the *ratio decidendi* is not modified on appeal then the UK legal position will allow for patents on DNA sequences to extend to all processes using the gene from which they were once derived. For instance, under this judgment, the Kirin patent could be infringed by a drug which would be found to activate endogenous Epo production. In addition, on infringement proceedings, causal links between patent disclosure and the development of new inventive technology could be taken into account, in breach of the fundamental principle that patent disclosure should promote progress. Finally, one would reach a situation where infringement proceedings can protect products and processes which were not claimed on a proper construction of the claims and could never have been claimed expressly because they were far too broad in scope.

The Biotechnology Directive II – overlapping DNA sequences

Recital 25 of the Biotechnology Directive provides that where the claimed DNA sequences in two patents "overlap only in parts which are not essential to the invention, each sequence will be considered as an independent sequence in patent law terms".

While the recitals are not legally binding, they provide very valuable insight into the intention of the legislators and this recital has a very profound effect on the protection of DNA inventions. It provides that notwithstanding that two product patents claim sequences that overlap, if the overlap is not essential for the purpose of the invention, then there will be no finding of infringement. This affects both express claims to a sequence (discussed in the previous section) and the protection of sequences by infringement law (discussed in this section).

This recital limits product claims to the parts of the product which are essential to the invention. This necessity test is an unknown function but is clearly based on the purpose or the utility of the invention.[100] This could conceivably result in a finding that most sequences

[96] *Improver Corp v Remington Consumer Products Ltd* [1990] FSR 181.
[97] *Kirin-Amgen Inc. v Roche Diagnostics GmbH* [2002] RPC 1; however, if the sequence was defined by a hybridisation test then the sequence variation would be disregarded.
[98] *Ibid.*
[99] Patent World, June/July 2001 p 9, Hiroshi Sheraton.
[100] In an earlier form of the Directive the requirement for overlap in non-essential sequences was absent and the effects were even more far-reaching. OJ C 286 Vol 40 p 87.

do not overlap in patent law terms unless they are put to the *same use*.

It is submitted that Recital 25 constitutes a restriction on the scope of DNA product patents based on their disclosed function.

The protection of the variations of patented DNA sequences, full-length sequences and gene homologues

Because of the Biotechnology Directive it is now unclear whether patents on genomic DNA or cDNA would protect the corresponding proteins or other direct derivatives of DNA such as mRNA or other variants of the sequences.

Conceivably, the Directive could result in the protection of allelic or engineered variations of claimed genes because they can be construed as the products of divergent propagation or multiplication. This is, however, unlikely to have been the intention of the legislators.

Similarly, by virtue of Article 9 of the Biotechnology Directive, a full-length gene sequence could infringe an EST (gene fragment) because the genetic information of the latter is "incorporated" in the former. It is submitted that "incorporation" within the meaning of the Directive is by technical means and not by virtue of being naturally part of a sequence. Therefore, a natural longer sequence would not infringe a smaller one unless designed specifically to carry it. In addition, Recital 25 indicates that the two sequences should be treated as separate inventions.

The protection of genes in species different from that in which they were patented is a different matter. It cannot be said that these genes are the product of divergent propagation (save if one considers the matter in evolutionary terms over millions of years). It is therefore unlikely that the Directive can be used to claim genes across species.

However, the doctrine of equivalents as developed in the United Kingdom by the *Kirin* case could lead to a court holding that alleles of a gene or a homologue in a different species are the equivalent of each other, if used for the same purpose or if they result in a similar or identical protein. The *Kirin* case, however, is controversial and will be appealed.

Conclusion

The implementation of the Biotechnology Directive has the potential to change dramatically the established principles of patent protection and infringement in the EU.

Its wording lacks clarity, but seems to have had as its purpose to extend as far as possible the scope of biotechnological patents. As the Directive is without prejudice to general principles of patent law,[101] it can be assumed that the normal principle whereby the protection granted by a patent must be commensurate with its technical contribution is maintained. It follows that all the limits to the scope of patents discussed in the previous sections are still good law and will limit the more permissive interpretations of the Biotechnology Directive.

Problems with Standard Product Patents

An inventor wanting to patent a DNA invention has at his disposal several approaches when delineating his claims. He could use a single sequence for his claimed DNA or protein. Any variation on that sequence would not infringe literally his patent. He would have to rely on the doctrine of equivalents for protection. This is uncertain both for the patentee and for any worker using sequences similar to that of the patentee.

Therefore a prospective patentee will typically attempt to "ring-fence" his invention by expressly setting out claimed variations on the sequence. This can take the form of setting out a homology threshold. As discussed previously, this approach creates problems with enablement, clarity and inventiveness.

Such claims are also uncertain from the standpoint of a worker trying to operate in the technical field of the invention while staying clear of its claims. This was a problem in the *Chiron NANBV* case, T188/97 as it was difficult to know which products fell within the claim. In fact a meaningful homology percentage can vary according to genes or species. Even homology is uncertain as one should define across which region to test. Certain regions in genes are highly conserved while others are very variable. Therefore one cannot even judge at the examination stage what is a relevant homology that will guarantee that most of the claimed sequences can perform even similar functions.

Alternatively, the patentee may try to supplement his sequence with a functional definition. This is risky and uncertain for a patentee. This is even less certain for a worker reading the patent claims in order to ascertain whether he is infringing as he may have to try to work the invention to determine whether his sequence can be used for the patented purpose and thus is infringing (see the *t-PA* case[102]).

It cannot be a satisfactory situation when litigation is necessary to map out the boundaries of a right. Any person should, on the face of a published patent, be able with certainty to avoid infringement.

---

[101] Recital 34 of the Biotechnology Directive, *supra*.
[102] T923/92.

It must be understood that the problem is not with the drafting of the claims or the EPO case law or with the technology. Rather it is in the very nature of DNA. All DNA sequences are made of four chemical bases arranged in varying sequences. They always have the same chemical structure; it is only the minor changes in the sequence which are responsible for the diversity of the coded proteins and thus of their effects. Small changes in a sequence can have great consequences (a single mutation can cause a disease such as cystic fibrosis). On the other hand, in some gene regions, large changes have no effect. One simply cannot know in advance.

Conventional structural claims in chemistry relied on the fact that chemicals have very diverse structures and that if structures were similar, then they had similar effects. One could look at a claimed structure and be confident that all compounds claimed would behave chemically in the same way.

The ability of genes and proteins to perform various functions makes functional claims also uncertain and results in complex biochemical tests to ascertain whether a candidate protein has, or not, a given function or property.

A product claim requires a structural or a functional claim (or a combination). Because of the very nature of DNA, product claims are not appropriate to this subject-matter. They will always lead to uncertainty which can only be resolved by an arbitrary rule or a ruling which will rest entirely on its facts and cannot easily be extended to a different situation.

Product patents on DNA will, as they become more common, lead to uncertainties as to the scope of the patents. It may not be possible at the examination stage to make any assessment, as only the patentee has detailed experience of his invention. The Opposition Division of the EPO would not have access to precise information and experimental knowledge of it. Only litigation could address the issue, but at the cost of uncertainties and delays.

Apart from problems with certainty, product patents have further implications for competition. Assume that a patent has been granted because these problems were disregarded or that the definitions were sufficiently precise to overcome these problems. The patentee would now have a patent on a sequence which may appear in different genes (because it is a feature of gene evolution to generate similarities in sequences, owing to the fact that genes evolve by copying parts of other genes), giving him commercial control on other genes. Even if it is argued that the patent is implicitly restricted to sequences that are usable in the invention, this is still uncertain. A patentee could threaten infringement proceedings against financially weaker alleged infringers. This is sufficient to give an unfair advantage to the said patentee. The legal delays will translate into delays in medical advances.

Even if the patent only claims more or less the same gene and variations thereof, this will still lead to unfair results. Consider the situation where a patentee has isolated a sequence by mass automated screening, then through the use of gene chips which greatly facilitates the screening of the expression of thousands of genes, the patentee has identified a marker for a disease. This is inventive as it is an unexpected result and a patent can rightly be granted. Another worker may actually do the difficult work of finding a cure for the disease using gene therapy. The second inventor could not obtain a patent on the sequence but only on the use of it. His patent is subject to obtaining a licence from the first patentee to avoid infringing. This situation was considered by the USPTO in a consultation exercise and was deemed fair.[103] However, one cannot agree. The main contribution to technology came from the second patentee. In addition, in EU competition law there are very few limits on a patentee's anti-competitive actions.[104] He can restrict supply and overprice without exposing himself to a finding of abuse of a dominant position or of anti-competitive practices. The original patentee who has done the less inventive work will control the patents of all subsequent inventors by virtue of the fact that he has an absolute product patent.

Such a situation is a hindrance on technological progress, progress which is the fundamental aim of patent rights.

It is submitted that the solution to these problems is to be found in the restriction of pure product patents for DNA inventions. Under such a regime there would be no product patents on DNA sequences which are derived from naturally occurring ones without substantial qualitative modifications. This could be legally achieved by deeming that the subject-matter (the product) is not novel.

This approach would solve many of the problems associated with product patents.

A patent claim would need only to disclose the starting material (being the sequence) and enable its industrial use. No complex definition of the claimed subject-matter would arise. Consequently, the problems with clarity would be reduced.

There would be no infringement merely because of sequence similarities or overlap. A finding of infringement would only arise where the industrial uses were equivalent, which can be judged easily. Such a regime would bring certainty from the point of view of a worker who needs to establish easily whether he is operating in the forbidden area of a patent.

As a result, DNA patents could be independent while using the same sequences (as is envisaged by Recital 25 of the Biotechnology Directive). One patent using a given sequence would not be subject to another one using a similar sequence and both would rank equally.

The problems associated with claiming sets of sequences for enablement, clarity, inventiveness and unity would not arise because it will not be the sequences that are claimed but their industrial applications. Only enabled uses of the sequences would therefore be protected. The

[103] See Federal Register Vol 66 No 4, January 2001 p 1092.
[104] *Volvo AB v Erik Veng (UK) Ltd* [1989] 4 CMLR 122; *CICRA v Renault* [1988] ECR 6039; and *Chiron Group v Organon Teknika Ltd (No 2)* [1993] FSR 324.

sequences would be disclosed only as starting material and the fact that some members of this class do not possess the properties necessary for the invention would be of no consequence.

In the still rare cases where through genetic engineering the resultant DNA sequence is qualitatively different from any natural counterpart (such as with engineered mutations or chimeric proteins), allowing a pure product patent on a well-defined sequence would be fair. The only function of the sequence would be what it was engineered for and the doctrine of equivalents would prevent non-literal infringement.

These suggestions may appear drastic but there is support among patent attorneys for this position.[105] In addition, it is already envisaged, firstly by the EPO which is prepared to construe and thus restrict a product claim to its enabled industrial application (by construing the claim in the light of the description) and secondly by Recital 25 of the Biotechnology Directive which envisages that two overlapping sequences may not infringe each other if they are patented for different uses. These two positions taken together indicate that the EPO may move towards a regime where patents are allowed on products but only to the extent of their disclosed industrial use. It is submitted that such a position is tantamount to a weakening of product patents.

Conclusion

The EPO, as can be judged from the Trilateral Projects and the incorporation of the Biotechnology Directive, is taking a strict approach in respect of the requirement of industrial application. There still remain uncertainties even after the Biotechnology Directive, notably in relation to industrial function. The EPO's requirements on unity, sufficiency, clarity and inventiveness appear, however, less strictly applied than could be expected from an analysis of the Trilateral Projects and the EPO case law, when applied to open-ended claims to a range of sequences.

The EPO appears willing in some circumstances implicitly to construe and restrict claims to what is enabled and contained in the description. However, the legal basis and scope of this approach are uncertain owing to contradictions in the case law.

The Biotechnology Directive (Recital 25) and the application of construction rules to the claim (Article 69(1) EPC) have thrown some doubts on the precise scope of biotechnology patent claims and their protection. There is a real possibility that the EPO is moving towards a regime where product claims are implicitly limited to the processes that they enable.

This writer has argued that DNA and genes being structurally homogeneous and essentially information vectors, product patents are inappropriate for DNA sequences. A widespread patenting of sequences will lead to uncertainties in the scope of the claims and to litigation, with the inevitable unfairness of the first patentees gaining a stranglehold on this area of technology. It must be stressed that this position is not borne out of an argument against the patentability of genes but arises from the legal impracticalities of having product patents claiming overlapping sequences.

The fact that such a proposition appears to be going against established principles should not be a deterrent. Patent law evolved to ensure progress and competition. If, within the current legislative framework, it cannot promote these functions, then there should be no impediments to change. Such changes can only be effected at the level of the EPC members and the EU as any regional fragmentation of the law can only make this field more uncertain.

The promises of this technology are great and must be allowed to develop in a fair, competitive and certain intellectual property framework, which can only be achieved through European-wide legislation and the establishment of a single appellate jurisdiction.

---

[105] *Gene patents: a different approach* [2001] EIPR 505, Philippe Jacobs and Geertrui Van Overwalle; and *Gene and compound per se claims: an appropriate reward?* [2000/2001] 6 BSLR p 239, Alan W. White.