

## DNA: the European way

*The impact of the Biotech Directive*

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IN SUMMARY

- The unique property of DNA raises a number of questions in patent law
- Some of these questions have been addressed by European Directive 98/44/EC but questions still remain about its interpretation and implementation
- The directive confirms that gene sequences can be patented, but an industrial application must be specified. The industrial applicability criteria has been interpreted differently by EU member states
- For now it is not clear whether genetic information will receive *per se* protection across Europe

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# Protection for DNA-based claims in Europe

## Varying attitudes adopted

**Dr Matthew Royle, an associate, and Dr Gareth Morgan, a partner in the Intellectual Property Department of European law firm Taylor Wessing examine EU member states' differing approaches to DNA-based patents**

**D**eoxyribonucleic acid (DNA) is not an ordinary molecule. It consists of two complementary strands which are made up of just four bases: adenine, cytosine, guanine and thymine. Depending on the order in which the bases occur (the DNA sequence), the DNA can cause different effects within the cell. But the DNA itself is not the effector molecule, it is an information vector that is passed from one generation to the next and, in the hands of a biochemist, from one organism to another. Before it can have an effect, DNA must be transcribed into messenger ribonucleic acid (mRNA). The mRNA then leaves the nucleus and is translated into the corresponding protein by ribosomes. The resulting polypeptide chain is likely to undergo further modification and processing before the final effector molecule is produced. So the DNA molecule has no structural relationship with the effector molecule. It does, however, contain all the genetic information needed by the cell to create it and, indeed, is necessary for the effector molecule to be produced. In this respect it differs markedly from new chemical entities that exhibit pharmaceutical activity themselves.

The unique property of DNA raises a number of questions in patent law. In particular, if a valuable effect is identified, what protection should be given and what conditions should be attached to providing this protection. Should, for instance, a patent protect the DNA molecule itself? In the vast majority, if not all cases, DNA molecules are identified and sequenced from nature and are therefore discoveries rather than inventions. Should a patent and the corresponding 20-year monopoly be granted for a discovery? Conversely, is it justified to treat claims to DNA molecules any different to claims to new chemical entities? Some of these questions have been addressed by Directive 98/44/EC on the Legal Protection of Biotechnological Inventions (the "Biotech Directive") but questions still remain about the implementation and interpretation of this directive. In this article we look at the core legislation, the approach taken to DNA based claims in the UK and in Europe, and address the impact of recent decisions on future protection for patentees.

### The Biotech Directive

The Biotech Directive was passed on 30 July 1998 and was due to be implemented by member states by 30 July 2000. It was intended to clarify the law on biotech inventions and to introduce a consistent approach across Europe, because prior to its introduction, protection was available in some countries but not in others.



The biotech Directive confirmed that naturally occurring biological material could be protected once it is isolated.

However, in order to get protection over biological material, the patentee must disclose a specific industrial application within the patent application. This is effectively equivalent to the requirement in

section 1(1)(c) of the Patents Act 1977 (and Article 57 of EPC2000).

So, the law across the EU recognises: (a) that biological material can be patented (Article 3(2)); (b) that this includes gene (or partial gene) sequences (Article 5); but (c) that the industrial application must be disclosed in the application for DNA-based claims to be allowed (Article 5(3)). The question then remains what disclosure is sufficient to satisfy the industrial applicability criteria, how such claims will be interpreted and what protection they will offer. It is the interpretation of these points that still varies between different member states. For instance, although it is not required by the Biotech Directive and is not the case in many member states, in France and Germany, only purpose-bound protection is available, as the industrial applicability cannot be separated from the gene sequence for the purposes of scope of protection.

### The position in the UK

The Biotech Directive was implemented in the UK on 28 July 2000 and applies only to patent applications filed after that date.

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The wording of the Biotech Directive has been preserved in the UK and is set out in Schedule A2 to the Patents Act 1977.

Despite being in force for some eight years, no patents covering biotechnological inventions to which the Biotech Directive applies have yet been considered by the UK courts to date. It is necessary therefore to look at case law decided

outside the scope of the Biotech Directive to see how claims to biological material might be interpreted. Even so, the number of cases considering pure claims to DNA-based inventions in the UK is relatively small.

*Biogen v Medeva* [1997] RPC 1 related to the expression of Hepatitis B viral antigens. The claim in issue was to a recombinant DNA molecule. Recombinant DNA is not found in nature.

As such the claim is not to naturally-occurring DNA per se. Rather, it is to recombinant DNA, which is DNA that has been produced in a particular way (combinations of DNA strands that would not normally be found together) and characterised by production of a polypeptide displaying HBV antigen specificity. The invention here is not, therefore, a mere discovery of a naturally-occurring DNA sequence. Indeed, the point of the invention was that it could be used without knowledge of the DNA sequence of the viral antigens – one of the experts drew an analogy that working without knowledge of the sequence was like working with the lights off and that Biogen had simply invented a way of working in the dark. Once the lights were switched on (the DNA sequence was published), there was no need to use this method.

Famously, the claim was held to be insufficient because it claimed more than the patent’s technical contribution to the field, but because it does not claim a naturally-occurring DNA sequence, *Biogen* does not assist greatly when considering the scope of protection given to DNA based inventions.

The House of Lords decision in *Amgen v TKT* [2005] RPC 9 was handed down after the implementation of the Biotech Directive. There is no mention of the Biotech Directive in the decision and no suggestion that it applied to the patent in suit but the reasoning of the court is remarkably consistent with what one might expect under the Biotech Directive. In *Amgen*, claim 1 was to a DNA sequence for use in securing expression of erythropoietin in a host cell.

Whilst claim 1 itself was not infringed because TKT made erythropoietin outside the UK, its interpretation was an important part of the case since Amgen alleged infringement of claim 26 which claimed erythropoietin produced by the DNA sequence of claim 1. It was therefore necessary to construe claim 1 in order to understand claim 26.

The court was clear that the sequence of the erythropoietin gene contained in table VI could not be the invention as it was a mere discovery. Lord Hoffmann concluding<sup>1</sup> that “it cannot be right to give

*[the patentee] a monopoly of the use of the information as such.”*

The facts of this particular case are instructive. The patentee had sequenced the gene for erythropoietin and claim 1 covered its expression in a host cell to produce the erythropoietin protein (claim 26 covering the product of this expression). The alleged infringer, TKT, made use of a process called homologous recombination to insert a promoter in front of the endogenous erythropoietin gene which caused an overexpression of the protein and allowed increased yield. The important question was what was meant by “host cell” in claim 1? The court construed this to mean that the erythropoietin DNA must be exogenous. In other words, protection was not given to the DNA sequence per se (the

information in the quote from Lord Hoffmann) as TKT's process no doubt made use of the same sequence. Protection was given instead to the method of producing erythropoietin – or would have been had the claims been valid.

TKT must have made use of the sequence disclosed in the patent in order to design a suitable targeting construct to use to introduce its high expression promoter in front of the erythropoietin gene by homologous recombination. However, homologous recombination was not a method contemplated in the patent and Amgen could not have a monopoly over the information.

Disclosure of an industrial application for erythropoietin was not needed because it was already being used at the date of the patent so an industrial application was inherent in the disclosure.

In the recent case of *Monsanto v Cargill* [2007] EWHC 2257 (Pat), claim 1 was to an isolated DNA sequence encoding a Class II EPSPS enzyme. As such it was closer to a claim to a specific DNA molecule than either of the claims in *Biogen* and *Amgen*. Here, the complication was whether there was infringement and whether this infringement actually used the invention of the patent.

Cargill imported soymeal from genetically modified soya beans into the UK. Monsanto has a patent to the gene sequence that conferred resistance to the herbicide glyphosate (Roundup) on the soya plants from which the soymeal was derived, and sued Cargill for infringement of this patent. The judge found as a fact that the gene sequence was present in the imported soymeal so the DNA molecule claimed was present in the allegedly infringing material. However, because of the judge's construction of the claim, the patent was not infringed.

In particular, Pumfrey J held that the term "isolated" was a technical term that applied to DNA sequences that had been removed from a genome and were in a form ready for further processing. The DNA within the soymeal was not in such a state, although it could be isolated from the soymeal and used in a way envisaged by the patent.

Pumfrey J based this construction on expert evidence but also referred to the structure of the claims, which essentially set out the process of isolating the DNA sequence, making a DNA plasmid, transforming plant cells, making a glyphosate resistant plant and then using

it to improve yields in the field. When put into this context, it is clear that the early claims relate only to laboratory work and require the DNA to be "isolated" within the meaning given to it by Pumfrey J. The word "isolated" does not appear in the later claims.

This interpretation of "isolated" precludes per se protection for the sequence within a cell as it will not be "isolated". It is, however, important to note that had Monsanto been successful in its

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submissions as to the construction of Class II EPSPS enzyme, it would have had per se protection over the recombinant DNA molecule (including a promoter, the structural DNA sequence and 3' non-translated region) because there was no restriction in these claims to the DNA being isolated.

The most recent biotechnology case to be decided in the UK was *Eli Lilly v HGS* [2008] EWHC 1903 (Pat). In this case, the claim was to an isolated nucleic acid molecule encoding a neutrokin- $\alpha$  polypeptide. Although in this case, "isolated" was a defined term within the specification of the patent and the parties did not dispute this interpretation so its meaning was not considered.

Kitchin J recognised that the Biotech Directive did not apply to the patent in suit, but the parties had accepted that the implementation of the Biotech Directive had not changed the law so, unlike the cases discussed above, Kitchin J's judgment considered the requirements of the Biotech Directive, at least as regards industrial

applicability. Kitchin J reviewed the jurisprudence that has developed in the UK, in the EPO and in the US on whether an industrial application was disclosed in the patent. From this review, it is clear that the jurisprudence of these three jurisdictions is consistent and requires a sound and concrete basis for recognising the industrial applicability rather than an interesting research result that could lead to an industrial application in the future. Since this is the first opportunity that a court has had to consider the issue of industrial applicability, it was important that Kitchin J took the opportunity effectively to rubber stamp the approach that has been taken by the EPO and the UKIPO in recent years.

### **The position in EPO and around Europe**

As mentioned above, not all jurisdictions have necessarily interpreted the Biotech Directive in the same way when implementing it into their national laws.

The EPO is not a member of the EU and therefore was under no obligation to implement the Biotech Directive. Nevertheless, Rule 26 requires that it is used as a supplementary means of interpretation. Furthermore, Rule 29 sets out the wording of article 5 of the Biotech Directive preventing speculative patents covering poorly characterised genes being granted by the EPO because the application as filed must provide a credible utility for the gene: the EPO's approach to this was reviewed and approved in *Lilly v HGS*.

Claims to gene sequences per se are granted by the EPO if industrial applicability is disclosed in the specification. What is not clear, and is not the concern of the EPO, is how these claims will be interpreted in the national courts.

For instance, in France, it is stated in statute that the sequence or partial sequence of a gene is not patentable per se. Instead, only the technical application of the gene sequence, which must be fully disclosed in the patent application, is protected.

Similarly, in Germany, the industrial application of a full or partial gene sequence must be fully described in the patent application. Moreover, the German provisions go further and in the case of sequences or partial sequences of human genes, the function must be included in the claim.

## Derivative products

An interesting case study into the differences in implementation and interpretation of the Biotech Directive in different jurisdictions around the EU is provided by related litigation brought by Monsanto in the UK, the Netherlands and Spain. The facts of *Cargill v Monsanto* in the UK have been set out above. Monsanto also alleged infringement on essentially identical facts against Cargill in Spain and against Cefetra in the Netherlands. Given the similar fact patterns, it is possible to assess how each country's interpretation of the Biotech Directive affects the result of the litigation.

The Biotech Directive does not apply to the patent in suit in the UK whereas it does in Spain and the Dutch court proceeded on the basis that it does in the Netherlands. This in itself suggests that potentially different results might be achieved in different jurisdictions, albeit that, with the passing of time, this wrinkle will disappear.

The reason why it could be important whether the Biotech Directive applies to this fact pattern is the limitation introduced by Article 9 of the Biotech Directive, which appears to limit protection to situations where genetic information performs its function.

Soymeal is highly processed and contains no viable cells. In these circumstances, the inserted gene, even if present, is not performing its function because, in order to perform its function, it would need to be transcribed into mRNA and then translated into an amino acid sequence and this can only happen within a viable cell. If the Biotech Directive applied to such a situation, there would arguably be no infringement due to Article 9. In Spain, the court held that the Biotech Directive applied and importing soymeal did not infringe Monsanto's patent for this very reason.

Given that the value of a gene sequence is the property of its transcription/translation product and in order to yield this product the DNA must be functional, it appears that this restriction will not be controversial in the majority of cases. After all, there is very little benefit (apart from perhaps with DNA vaccines) to be had from keeping a vial of isolated DNA on the bench until it is expressed in a cell. Where Article 9 does have an effect, as is demonstrated by Monsanto's various actions, is in respect of derivative products in which the genes

have performed their function but are no longer active because of some downstream processing of the cells. However, this situation may have been addressed by including a claim to soymeal to the claim set – particularly in this case as soymeal is one of the main products obtained from soya plants.

The decision in the UK is discussed above and Cargill were held not to infringe because of the construction given to the word "isolated".<sup>2</sup> It is interesting that the Dutch Court also adopted this construction of the word "isolated" and as a result found non-infringement.

Some commentators have criticised the construction given to "isolated" in the UK and in the Netherlands primarily because of the convention of its use in the US. In the US, patentees have to use "isolated" in their patent claims to distinguish the claimed sequence from that in nature. However, that is not the law in the UK and the Netherlands and including a word in the claims of a patent is important and must mean something to a person skilled in the art. As noted by Pumfrey J in the UK decision, the structure of the claims in biotech patents quite often reflects the process by which the invention is implemented. This is no doubt the case in the patent in suit in these actions. Were "isolated" simply to mean that a DNA sequence has been removed from its genome at some point in the past then the sequence would effectively have per se protection from the moment it was removed from its natural genome and lower claims to the ways in which the sequence is used would not be necessary. It must be right to construe "isolated" restrictively to avoid mass redundancy in such patent claim sets.

There are a number of claims in Monsanto's patent that are not restricted by the word "isolated". So, although the Dutch court found non-infringement of a number of claims as a result of its interpretation of "isolated", there are a number of claims remaining that must be interpreted in light of the Biotech Directive. For these claims, the Dutch court made a reference to the ECJ asking for clarification of the scope of Article 9 and to which patents the Biotech Directive applies.


When the ECJ answers these questions, the scope of Article 9 should become clear. The ECJ will address whether per se protection is available for DNA molecules. Currently the requirement in Article 9 for a DNA molecule to perform its function could

be interpreted to mean that protection is provided only to the expression of this function (transcription and translation). Such an interpretation would preclude per se protection so it is important that the ECJ clarifies the point.

Moreover, clarification of which patents the Biotech Directive applies to will be given and this might prevent the need for a series of challenges to late implementation of the directive by a number of member states.

## Summary

The UK approach to DNA-based claims in the most part has not given per se protection to the claimed DNA sequence, although this could simply be due to the wording of the claims litigated in the UK so far. Claims are being granted by the EPO that cover the DNA molecule per se on the condition that a real industrial application is disclosed in the specification so it is important that the scope of protection afforded to such claims is clarified. Currently, what protection is given by these claims will vary in different countries. In the UK it seems following *Monsanto v Cargill* that per se protection is available for "isolated" DNA and for recombinant DNA in any state. A similar position might also exist in the Netherlands, although much will depend on the reference to the ECJ. In Germany and France, however, it is likely that the protection given to claims to DNA sequences is purpose bound.

There also remains a degree of uncertainty over the effect that the Biotech Directive will have on this position. The patents to which the Biotech Directive applies are different in different countries and although this problem will correct itself with time, it might cause uncertainty for the next ten to fifteen years. The interpretation of Article 9 is also not clear and it seems that different member states have chosen to implement the Directive in different ways. For now it is not clear whether genetic information will receive per se protection across Europe. The response to the Dutch court's referral to the ECJ when it comes will be informative. 

## Notes

1. At \$77 of the judgment.
2. The judgment from the Netherlands (in English) is available on Holman's Biotech IP Blog ([http://holmansbiotechipblog.blogspot.com/2008\\_05\\_01\\_archive.html](http://holmansbiotechipblog.blogspot.com/2008_05_01_archive.html)). See, in particular, paragraph 4.4.