William Cook
is a specialist intellectual property solicitor, and advises clients on all aspects of IP protection, licensing and enforcement, with particular focus on patent matters. In recent years, he has advised and represented clients in several reported life science cases in the English High Court, including cases relating to novel pharmaceutical compounds, biotechnological inventions and modes of drug delivery. He is a member of Simmons & Simmons' pre-eminent Biotechnology and Pharmaceutical Practice Group, and advises clients on licensing and other commercial issues relating to patents and other areas of IP.

Keywords: *patent, construction, infringement, Amgen, equivalents, protocol*

William Cook
Simmons & Simmons,
One Ropemaker Street,
London EC2Y 9SS, UK

Tel: +44 (0) 207 825 4288
Fax: +44 (0) 207 628 2070
Email: william.cook@simmons-simmons.com

Amgen v TKT: Assessment of inventive concept is crucial for assessing infringement of biotechnology patents

William Cook

Date received (in revised form): 5th January, 2005

Abstract

In a landmark decision, the House of Lords in *Kirin Amgen v Hoechst & TKT* has confirmed the correct approach of proper construction of patent claims, as interpreted in the full light of the invention, to assess infringement. There is no 'doctrine of equivalence' under English law: variants falling outside a patent claim cannot infringe that claim, even if they are somehow 'equivalent' to the claimed invention.

INTRODUCTION

On 21st October, 2004, the House of Lords gave its judgment in the biotechnology case of *Kirin-Amgen Inc and others v Hoechst Marion Roussel Limited and others* 2004 WL 2330204, which contains a careful restatement of the correct approach to the assessment of patent infringement in UK courts. In construing a patent claim, much more emphasis must be placed upon what the skilled person would have understood a patentee to mean by the language of the claims, especially of 'new technology' patents, than the traditional sole reliance on the three 'Protocol' or 'Improver' questions. Patent practitioners, who have been wedded to the Improver questions as structured guidelines in assessing infringement for the past 15 years, will need to address the substantive nature of the invention as claimed more carefully in the future.

The judgment also clarifies the correct approach in the UK to the novelty of 'product-by process' claims. Such claims will be novel only if the product itself is new: a product-by-process claim may only be used where the product cannot in practice be defined by reference to its composition (for example, where novelty of the product arises from the process of manufacture and the product is defined by that process). Finally, the judgment gives some further guidance on when a patent is 'sufficient' for the purposes of patent law, especially in the context of biotechnology inventions.

Lord Hoffman gave the leading judgment of the Court, unanimously approved by the other four Law Lords who heard the case. His clarification of the patent infringement test that he himself propounded 15 years ago in *Improver Corporation and others v Remington Consumer Products Limited and others* [1990] FSR 181 is particularly interesting, especially his critical comments as to when that test may be of use. The judgment's emphasis upon the primary importance of the claims, as interpreted in accordance with Article 69 of the European Patent Convention, using the Protocol on Interpretation of Article 69, brings the UK's approach to claim construction closer to that in Germany, the Netherlands and other continental European jurisdictions. At a time when the proposals for a European Community-wide patent system are floundering at inter-Governmental level, European convergence on claim construction is already happening.

BACKGROUND

Kirin-Amgen (Amgen), the Californian biotechnology company, owned a European patent relating to the production of the protein erythropoietin (EPO) by recombinant DNA technology. EPO is a hormone made in the kidney which stimulates the production of red blood cells by the bone marrow.

Amgen sued two other biopharmaceutical companies, Transkaryotic Therapies Inc. (TKT) and Hoechst Marion Roussel Ltd (Hoechst), alleging that TKT's method of making EPO infringed the patent. TKT used a process which it calls 'gene activation', the resulting form of EPO being referred to as GA-EPO, and Hoechst proposed to import GA-EPO into the UK. TKT and Hoechst both counterclaimed for revocation of the patent (and no distinction between them is made in the judgment).

Both infringement and validity were considered by the court

THE PATENT

The technology for manufacturing proteins (polypeptides) by recombinant DNA techniques developed rapidly after the mid-1970s. However, it was difficult to make EPO in the early 1980s because its structure (amino acid sequence) was unknown, and it was difficult to get hold of enough of natural EPO to sequence it. The Amgen team obtained a small amount and, surprisingly, were able to locate and identify the EPO gene in 1983.

Once known, it was then possible to make EPO by known methods of recombinant DNA technology, as described in the patent:

> a gene that specifies the structure of a desired polypeptide product is either isolated from a 'donor' organism or chemically synthesised and then stably introduced into another organism which is preferably a self-replicating unicellular organism such as bacteria, yeast or mammalian cells in culture. Once this is done, the existing machinery for gene expression in the 'transformed' or 'transfected' microbial host cells operates to construct the desired product, using the exogenous DNA as a template for transcription of mRNA which is then translated into a continuous sequence of amino acid residues.

Amgen's patent required the expression of EPO in a 'host cell' using specified DNA sequence(s)

Amgen isolated the gene that coded for human EPO from a human donor cell and then introduced it into a mammalian cell (from a Chinese hamster) which divided and produced EPO in culture. As part of cultured hamster cells' DNA, the expressed EPO was coded by the exogenous, or introduced, human EPO sequence. The process was much more complex than this, of course, but such complexity involved only techniques that were well known among skilled persons at the time. In essence, the new process was the introduction of an exogenous DNA sequence (which coded for EPO) into a host cell in which it would be expressed.

From the 31 claims in the patent, the Court only needed to assess claims 1, 19 and 26. In summary, these claims are for (1) a DNA sequence for use in securing the expression of EPO in a host cell, such sequence selected from tables in the patent or related sequences; (19) EPO which is the product of the expression of an exogenous DNA sequence, and which has a higher molecular weight by the 'SDS-PAGE' (sodium docecyl sulphate polyacrylamide gel electrophoresis) testing method than existing EPO derived from extraction from urine; and (26) EPO which is the product of the expression in a host cell of a DNA sequence according to claim 1. Only claims 19 and 26 were alleged to have been infringed because TKT do not make any GA-EPO in the UK, and so do not use or import a DNA sequence according to claim 1 – the alleged infringement was importation of EPO according to claims 19 and 26.

THE ALLEGED INFRINGEMENT: TKT'S GENE ACTIVATION METHOD

In TKT's method, the EPO is expressed in cultured human cells by an endogenous

gene naturally present in the cells. Ordinarily, such a gene would not express EPO – almost all human cells contain the full complement of DNA coding for all the proteins needed by the body, but each cell will express only those proteins that its particular tissue requires: the rest remain inactive. The TKT technique involves introducing some necessary control sequence (some other exogenous DNA), at exactly the right point upstream of the EPO gene itself. This could not have been done at the time of the patent but can be done now, by 'switching on' the EPO gene in the cell and enabling the expression of the EPO protein.

TKT's method introduced an exogenous control sequence activating endogenous DNA

The essential difference between the patent and the TKT process is that the former is made by an exogenous DNA sequence coding for EPO which has been introduced into a host cell, and the latter is made by an endogenous DNA sequence coding for EPO in a human cell into which an exogenous upstream control sequence has been inserted.

THE HOUSE OF LORDS' DECISION

The court below, the Court of Appeal, had held that both claims 19 and 26 were valid but that neither was infringed. Both sides appealed in the House of Lords: Amgen argued that, as a matter of construction, the TKT process fell within both claims; and TKT argued that both claims were invalid for insufficiency and claim 26 was invalid for lack of novelty.

Construction

The correct approach is to ask what the skilled person would understand the Patentee's intention was

Whether a patent is infringed or not depends upon whether the alleged infringement has all the features of a claim or claims of the patent. But the precise identity of those features depends upon how they are described in the claims. Whether an alleged infringement contains a particular feature as described is often a subject of argument, requiring the court first to 'construe' the claims, then to assess infringement of the claim pursuant to that construction.

The House of Lords in *Amgen* took the opportunity to analyse the approach taken in the assessment of infringement and claim construction by the Courts in the UK and the other Contracting States to the European Patent Convention (EPC). The most important provision is Article 69 of the EPC, which has been incorporated into the laws of all Contracting States:

> The extent of the protection conferred by a European patent or a European patent application shall be determined by the terms of the claims. Nevertheless, the description and drawings shall be used to interpret the claims.

The settled approach of the English Courts is to give patent claims a 'purposive construction', being what a skilled person would have understood the patentee to be using the language of the claim to mean (*Catnic Components Limited and another v Hill and Smith Limited* [1981] FSR 60). In the present case, the House of Lords approved this general approach, that is to say a 'purposive construction'.

Since 1989, the approach has normally been broken down by following a three-part set of guidelines (the three 'Protocol' questions) set out in *Improver v Remington*, where an alleged infringement contains a variant falling outside the primary, literal or acontextual meaning of a claim. In such cases, the Court assessed (1) any material difference between the variant and the way the invention works, (2) the obviousness of such difference and (3) whether strict compliance with the literal meaning was essential. It was thought that following these guidelines ensured that claim construction in the UK complied with the provisions of Article 69 and the Protocol.

However, the House of Lords in the present case held that the three 'Protocol' questions were no substitute for the fundamental approach. The fundamental approach constitutes trying to understand what the person skilled in the art would have understood the patentee to mean by the language of the claims – this approach

is a purposive construction. In fact, whether the Protocol questions will be of use will depend on the nature of the invention – they will be of use when claims are defined in terms of parameters (measurements, angles and the like), as was indeed the case in Catnic. But they are unlikely to be useful in rapidly developing technologies such as biotechnology or semiconductor electronics. Put simply, if they are used after the proper scope of the claim has already been defined according to a purposive construction, they are unlikely to add anything further. Something outside the claim properly construed should not fall within it after consideration of the Protocol questions, nor vice versa.

The House of Lords found it essential that the DNA sought should not come from the genome of the host cell

On the facts in *Amgen*, this issue was important because claim 1, and therefore claim 26 by extension, required the expression of EPO in a 'host cell'. The chief question of construction was whether the skilled person would understand 'host cell' to mean only: (1) a cell which is host to (ie recipient of) an exogenous DNA sequence which coded for EPO (which would mean that TKT's process did not use such a host cell and so did not infringe); or whether it should extend also to (2) a cell which is host to any exogenous DNA, as long as the cell includes an EPO sequence which is endogenous to the cell (which would lead to infringement, as TKT's does use such a cell). In the TKT process, the cell is host to the control sequence and other machinery introduced, but not to an exogenous EPO sequence.

On the evidence, at first instance in the High Court, the judge held that the claim referred to a sequence coding for EPO which was exogenous to the cell in which expression took place. The judge said that 'a cell is not a host cell unless it is host to exogenous DNA encoding for EPO or its analogue'. His conclusion was based on the teaching of the patent, in which the terms 'host' and 'host cell' are used consistently to describe cells that have been transfected with exogenous or foreign DNA (ie DNA from outside that particular cell) that encodes EPO, with a view to securing expression of EPO in those host cells. The specification also used the wording 'for use in securing expression . . . of a polypeptide' which suggested that the DNA introduced coded for that polypeptide rather than a control sequence which promoted expression of endogenous DNA. Also, when discussing the use of mammalian cells which already have an EPO gene of their own, the specification stated that 'expression of, eg, monkey origin DNA in monkey host cells . . . actually constitute instances of ''exogenous'' DNA expression inasmuch as the EPO DNA whose high level expression is sought would not have its origins in the genome of the host.'

As a result, the House of Lords concluded that the patentee regarded it as essential to its invention that the DNA of which high-level expression was sought should not have its origin in the genome of the host cell. This decision was based entirely upon the meaning of the term host cell, which is wholly dependent on the context of the patent.

Infringement

Assessment of infringement follows from proper construction of the claims. Unlike the USA, the UK does not recognise any separate concept of 'doctrine of equivalence'. In the USA, a variant outside a properly construed claim, which is otherwise 'equivalent' to that claim, will still infringe the claim. However, in the UK, 'purposive construction' defines claim scope: the question on infringement in the UK is then simply whether a product or process is described by that claim, properly construed.

In *Amgen* the House of Lords concluded that the skilled person would not regard the endogenous coding sequence which expressed TKT's GA-EPO as being the exogenous sequence effectively required by claim 1. Therefore GA-EPO itself did not infringe claim 26. Similarly, GA-EPO was not 'the product

of . . .expression of an exogenous DNA sequence' within claim 19, and so no claim was infringed.

In the House of Lords judgment, this is where the analysis should end. The claim had been construed 'purposively', and on the facts there was no infringement. It specifically disapproved of any further attempt (by the judge at first instance in the High Court) to apply the Protocol questions over and above that construction. The construction set out above was not a 'primary, literal or acontextual' analysis, but clearly an analysis in the context of the patent. To then look at a variant outside the claim as so construed, as per the Protocol questions, was meaningless. The conclusion is that 'purposive construction' shall not be used to support a US-style 'doctrine of equivalence' approach to infringement analysis.

The UK does not recognise a US-style 'doctrine of equivalents'

Novelty

Patents may only be granted for inventions which are (among other things) new. The House of Lords considered the novelty of 'product-by-process' claims, where a product is defined by its process of manufacture. The House of Lords overturned the existing law in the UK (that such claims may be novel if the process is new, even though the resulting product was known previously) and approved the practice of the European Patent Office. The approved practice is that, for such claims to be novel, the product itself must be new. A new method of manufacturing an existing product does not make the product itself new. It is only if the product is different, but the difference cannot in practice be defined by reference to its composition, structure or other testable parameter alone, that a product claim defined by the process of manufacture is allowable.

The House of Lords approved this as a matter of law, and in future the UK should apply the same test for novelty as the European Patent Office. In the context of the present case, there was no doubt that EPO as described in claim 19, on its face, would relate to something new, being EPO with a higher molecular weight by the SDS-PAGE testing method from existing EPO extracted from urine, although the sufficiency of such claim was another matter, as explained below. Claim 26 however was not new – as a matter of fact, the judge found that EPO made according to claim 26 was identical to the EPO which existed before the patent, and so under its newly approved approach, the Court found claim 26 lacked novelty.

In practice, this change in approach is unlikely to be of great importance because well-advised patentees will include process claims in their patents, which can be relied upon to allege infringement against 'products obtained directly by such process' under Article 64(2) of the EPC.

Insufficiency

To be valid, a patent must disclose an invention clearly enough and completely enough for it to be performed by a skilled person. The disclosure must enable the invention to be performed to the full extent of the monopoly claimed. Whether the specification is sufficient or not depends on the nature of the invention. The first step is to identify the invention and decide what it claims to enable the skilled person to do. Then one can ask whether the specification enables him to do it.

The House of Lords in *Amgen* considered four different issues relating to the question of sufficiency of the specification.

Breadth of claim

In the opinion of the House of Lords, the invention was the expression of EPO listing a specific recombinant DNA technique, not any technique using recombinant DNA. However, the House of Lords expressed sympathy with the view that, the broader a claim (covering many ways of making a certain protein), the more likely it is insufficient (the specification must disclose a way of

The Court will approach the issue of insufficiency based on the contribution the invention makes to technology

making it sufficiently generally to include all such processes). This is a classic patent law 'squeeze' against infringement – if a broader claim is sought to prove infringement, it is more likely to be insufficient. The House of Lords was asked to consider this objection on the assumption (against its ultimate finding) that the invention comprised the expression of EPO by any recombinant DNA technique (the 'broad' invention). As its ultimate finding was that the invention was narrower than this, the House of Lords view was not a 'concluded view'. On this basis, it held that claims relating to the broad invention would have been insufficient. In so doing, it approved its own comments in *Biogen Inc. v Medeva plc* [1997] RPC 1 that:

> If the invention discloses a principle capable of general application, the claims may be in correspondingly general terms . . . [I]f the patentee . . . has disclosed a beneficial property which is common to [a class of products] he will be entitled to a patent for all products of that class (assuming them to be new) even though he has not himself made more than one or two of them.

It concluded that, if the invention was not simply EPO itself but all methods of expressing it, the specification does not disclose a way of making it in sufficiently general terms to include the TKT process. It discloses only how to make EPO by introducing exogenous DNA coding for EPO into a host cell. The Court said that: 'The TKT method is not a version of this process which, although untried, could reasonably be expected to work just as well. It is different.' This decision highlights the Court's approach to sufficiency is based to a great extent on policy grounds. If the Court feels the patentee has made such a contribution to the technology as to deserve a broad protection, and the claims are drawn correspondingly broadly, it will more readily find that the claims are enabled across their full breadth, even if the specification itself provides only one example of the use of that technology.

The only proper conclusion is that, in future cases, the Court will approach the issue based on the contribution which it perceives that the patented invention has made to technology.

Analogues

The claims of the patent are directed not only to EPO but to all analogues which behave like EPO in promoting the manufacture of red blood cells. It was alleged that the patent is insufficient because it does not enable one to predict which analogues will behave like EPO. In *American Home Products Corporation v Novartis Pharmaceuticals UK Ltd (No.2)* [2001] FSR 41 the Court held that a patent was insufficient because it was not possible for the skilled man to assess whether any particular analogue had the relevant effect claimed by the patent (an immunosuppressive effect). Surely the same logic applied in the present case?

The answer is no. In the present case, the Court distinguished *AHP* on the basis that in *AHP* the invention lay in the discovery that a known product rapamycin (and possibly some of its analogues) had a particular immunosuppressive effect. But in *AHP*, the skilled person did not already know which derivatives had that effect – this would be new science and subject to testing – and the patent itself did not educate on the point. In *Amgen*, however, the invention did not consist of the discovery that EPO and some of its analogues promoted the formation of red blood cells (that science was already well known): the invention consisted of a way of making EPO and its analogues.

A claim to the production of a protein or its 'analogues' would be sufficient if the analogues were known and could be ascertained

The House of Lords also held that a claim to the production of a protein or its 'analogues' would be sufficient if such analogues were already known or could be ascertained by skilled persons. Only if a claimed product is itself new, and new 'analogues/derivatives' are also claimed, which would not be known to have the same properties, that such a claim would

be insufficient. On this aspect, therefore, the patent would have been valid, although the House of Lords was keen to stress that its decision on this aspect was not a 'concluded view'.

Cell varieties

The House of Lords also held that, even though the patentee disclosed in the specification only high-level expression of the protein in certain mammalian cells, the invention claimed still covered high-level expression in other cells. The House of Lords said that this kind of improvement did not need to be enabled by the specification.

It is interesting to contrast this finding with the decision in *Biogen v Medeva* where the technical contribution was making the relevant antigens in a prokaryotic host cell (simple cells present in bacteria), but the claims covered making them in any cell, including more complex eukaryotic cells (eg mammalian cells). Such broader claims would be insufficient in such circumstances. However, in *Amgen*, high-level expression was shown in one type of eukaryotic cell, and so the patent was not insufficient in respect of other eukaryotic and prokaryotic cells.

There is little that clever drafting of claims can do to get a broader scope of protection

These issues are unlikely to arise again. The *Biogen* specification referred to expression in prokaryotic cells because the techniques used in that patent were carried out in the late 1970s. Future cases are likely to be based on technology from the mid-1980s onwards.

Molecular weight

Claim 19 distinguished the EPO produced by the invention from existing EPO (see comments above concerning novelty) by claiming EPO having a higher molecular weight than existing EPO, when tested using a well-known testing method. After a review of much factual evidence on the point, the Court found this claim to be insufficient, as the molecular weights of possible existing EPO samples differed vastly due to the uncertainly of either their source or method of purification. The test for distinguishing EPO falling within claim 19 from existing EPO was incapable of application and the claim found to be insufficient as a result.

The Court disapproved of Amgen's attempt to 'patent the protein itself'

COMMENTARY

The outcome of the *Amgen* case is that neither claim is infringed, and the patent is revoked on the grounds that claim 19 is insufficient and claim 26 is anticipated. The House of Lords relied greatly upon the proper appreciation of the invention (ie the technical contribution to scientific knowledge) as being a particular way of expressing EPO. The conclusions of non-infringement and insufficiency followed inexorably from that.

So what can the biotechnology industry learn from the House of Lords judgment in *Amgen*? In fact, there is little that clever drafting of claims can do to assist patentees wishing to get a broader scope of protection than their invention properly supports. The Court's approach is clear – if the patentee stretches his invention too far, it is liable to lose future infringement claims as a result of a proper narrow construction in Court, or have its patent revoked for insufficiency or (as was the case in *Amgen*) both.

This of course conflicts with industry's general aim of drafting patents with as broad a set of claims as possible. In areas of doubt, patentees should ensure that subsidiary claims at least cover the narrower, more specific technology discussed in a patent as well as a broader claim 1 covering the patent at a more conceptual level. If claim 1 is revoked through insufficiency, at least the subsidiary claims may be retained.

The Court recognised that Amgen invented a perfectly good and ground-breaking process for making EPO and its analogues. However, it disapproved of what it saw as Amgen's attempt 'to try to patent the protein itself, notwithstanding that, even when isolated, it was not new.'

The Court's lack of enthusiasm for use of the three Protocol questions in assessing infringement is interesting. The Court's emphasis on the primary

importance of a purposive interpretation of the claims brings the UK's approach to claim construction closer to what is intended by Article 69 of the European Patent Convention and to the approach now being taken in Courts in other EPC countries.

Approaches to claim construction by European Courts are converging

In the last few years, rather than looking at the claims as a 'point of departure' for analysing infringement, the German and Dutch Courts seem to be approaching infringement analyses on the basis that the claims play a 'central role', and even the decisive basis for determining infringement. Just as the German Supreme Court (Bundesgerichtshof) has recently expressed that its approach to the question of infringement in a quintet of cases (*Kunstoffrohrteil* [2002] GRUR 511 and others) is similar to the *Catnic* approach, the House of Lords in *Amgen* has taken the opportunity to bring practice in the UK closer to that in mainland Europe. In all jurisdictions, identification of the full extent of the invention is the crucial step, and interpretation of the claim wording in context will be correspondingly broad (or narrow) as a result. Once the claimed invention is identified, assessment of infringement and sufficiency based on the claim wording, properly construed, will follow naturally.