Biogen v. Medeva – the highest court in the UK delivers judgement

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The highest court in the United Kingdom, the House of Lords, delivered its judgement in the case of Biogen v. Medeva on 31 October 1996. This case represented the first time that the House of Lords has considered a genetic engineering patent. The House of Lords had been expected to resolve a number of key issues of importance to biotechnology patents, including obviousness, insufficiency and width of patent claims. In this report, the authors review the House of Lords' decision and its implications.

The grant of a patent to an inventor gives that inventor an exclusive right to use his or her invention and to prevent others from doing so without a licence. In return for this monopoly, the inventor is expected to disclose his invention to the public. A patent therefore consists of two parts – the 'claims', in which an inventor defines his invention and sets its limits, and the 'specification', which should contain enough information to teach a skilled reader of the patent (such as a researcher in the relevant field) how to make or work the invention set out in the claims.

Patent criteria

For an invention to be patentable in the UK it must be:

- novel,
- inventive (i.e. non-obvious),
- capable of industrial application, and
- not excluded by statute (i.e. it should consist of patentable subject matter).

These criteria stem from the generally agreed concepts that a patent should not be granted for an invention that is already in the public domain, that would be obvious from what is already known, or that would be impractical. The statutory exclusions mainly relate to abstract or aesthetic concepts, such as pure discoveries, scientific theories or literary works, or inventions that may be considered immoral [a possible example of the latter, currently being considered by the European Patent Office (EPO), is the 'oncomouse'[1,2]].

Although the UK and European patent offices employ technical experts as examiners, in practice it is impossible for them to consider all relevant prior public knowledge before deciding whether to grant a patent. In addition, they do not necessarily have the time or specialist expertise to consider the patent specification in minute detail. Hence, a patent could be granted that is later found by the court to be invalid, usually because expert evidence subsequently reveals that the invention was not new or not inventive at the time the application for the patent was made or that the specification does not contain a sufficient description of the invention.

Scientific background

Much of the Biogen v. Medeva case revolves around what was publicly known in the genetic engineering and virus

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field in the late 1970s. At the time, recombinant DNA technology was in its infancy, and the use of non-bacterial hosts was virtually unknown. Hepatitis B virus (HBV) had been isolated, but only partially characterized. It was widely recognized, however, that if one could find a way to express its antigens in recoverable form, without using the virus itself, one would have the basis for a safe vaccine against the disease.

Unfortunately, at the relevant time, the HBV genome had not been sequenced and it was commonly thought that, because HBV infected only higher eukaryotic organisms, its genomic DNA would have introns and would not be expressed in a bacterial host. It was also unclear whether, as a general principle, eukaryotic genes could be expressed in bacteria. The only known eukaryotic DNA that had been expressed in a bacterium up to that date had been rat preproinsulin, but in that case cDNA (obtained by reverse transcription) had been used and, of course, cDNA does not contain introns.

In spite of these uncertainties, Professor Sir Kenneth Murray (Edinburgh University, UK) decided to attempt expression of HBV genomic DNA in bacteria, even though he had no knowledge of the DNA sequence. He used established laboratory techniques to cut the DNA using various restriction enzymes, ligate the fragments into pBR322 plasmids and screen transformed *E. coli* for expression of antigens. Although it was disputed at various points in the case, the House of Lords accepted that Professor Murray successfully expressed both the core and surface antigens of the virus. What Professor Murray did not do, because at the time the technology did not exist, was express either antigen in a non-bacterial host. Six months later, the HBV genome was sequenced and was found to contain no introns.

Legal background

In 1978, Biogen applied for a patent for a method of producing HBV antigens from recombinant DNA, based on Professor Murray's research. This patent formed the basis for a second patent application, which was filed at the EPO in 1979 and eventually granted in 1990. The latter patent covered the expression of both the core and the surface protein in any host (which would include bacterial, yeast and mammalian cells). In addition, it also covered DNA molecules coding for both surface and core antigens. Although opponents of the patent raised the issue of its validity at the EPO's own tribunal, the Technical Board of Appeal, the EPO finally found it valid on 28 July 1994.

Meanwhile, in 1992, Medeva announced plans to market an HBV vaccine and Biogen took them to court, claiming infringement of their patent. The first court in the UK to hear the dispute was the English High Court, where Judge Aldous (now Lord Justice Aldous) found that Biogen's patent was valid and had been infringed[3]. Medeva then successfully appealed to the English Court of Appeal, which found that the patent was invalid on the grounds of obviousness and insufficiency[4,5]. Subsequently, Biogen appealed to the House of Lords who, assisted unusually by two scientific advisers, heard the case in May and gave their decision on 31 October 1996 (Ref. 6).

Obviousness

Generally, obviousness is judged by identifying the inventive concept disclosed by the patent, comparing it with public knowledge, and deciding whether any differences would have been obvious steps to a researcher in that particular field at the time the patent was applied for. But what is the inventive concept?

In Biogen v. Medeva, Judge Aldous in the High Court defined the inventive concept as:

> the idea or decision to express a polypeptide displaying HBV antigen specificity in a suitable host.

On that basis, Judge Aldous found the patent was not obvious. He decided that:

> there is no evidence to suggest that anyone, other than Biogen, contemplated expression of HBV in December 1978, despite the fact that [knowing rat preproinsulin had been expressed in bacteria] there was an incentive to do so. The reason may well be that stated in the patent, namely that the skilled man was put off by introns.

The Court of Appeal took Judge Aldous's statement of the inventive concept at face value. However, they held that Biogen's patent was obvious, saying that, because eukaryotic DNA (rat preproinsulin) had already been expressed in bacteria, researchers would have thought of using Professor Murray's strategy to express HBV antigens, but would have 'regarded the odds as too long to justify the investment required'. The view of the Court of Appeal was therefore that this inventive concept was merely a commercial goal that had been shared by others in the field and the decision to adopt the method had been a commercial one:

> [Biogen had been] prepared to make the necessary investment of time and money ... nothing [Biogen] did was not obvious if you took the business decision to do it. Others considered the odds against success too long to justify trying ... [Biogen had made] a mere business assessment or choice to pursue an identified goal by known means.

To the relief of many industrial patentees (not just in the biotechnology sector), the House of Lords expressly disapproved the Court of Appeal's reasoning. The House of Lords held that such commercial considerations were irrelevant, saying:

> The fact that a given experimental strategy was adopted for commercial reasons, because the anticipated rewards seemed to justify the necessary expenditure, is no reason why that strategy should not involve an inventive step. An inventor need not pursue his experiments untouched by thoughts of gain. Most patents are the result of research programmes undertaken on the basis of hard-headed cost-benefit analysis.

Having said that, however, the House of Lords went further. The House of Lords agreed with the Court of Appeal that the inventive concept as identified by Judge Aldous was obvious because the idea was shared by others in the field, being the pursuit of an identifiable goal by known means (note that it was always Biogen's case that the idea was not shared by others in the field; if the House of Lords had accepted this, Biogen's patent may have been found to be valid). The House of Lords therefore redefined the inventive concept in terms of the particular problem that Professor Murray's invention overcame. The House of Lords held that the inventive concept could be redefined as:

> the idea of trying to express *unsequenced* eukaryotic DNA in a *prokaryotic* [i.e. bacterial] host (emphasis added).

The House of Lords said that by redefining the inventive concept in this way Professor Murray's invention was not a goal, but a method of achieving that goal. Therefore, the House of Lords were 'content to assume' that Biogen's patent would not have been obvious in 1978. Interestingly, the House of Lords held:

> the inventiveness alleged in this case is of a very unusual kind. It is said to consist in attempting something which a man less skilled in the art might have regarded as obvious, but which the expert would have thought so beset by obstacles as not worth trying.

Thus, the House of Lords overturned the Court of Appeal's finding that Professor Murray had chosen to pursue an identified goal by known means. By referring back to the problem that it required invention to overcome, a patent may be non-obvious as long as the method of obtaining the goal (albeit a known technique) was not an obvious choice. This could include a choice that others in the field may not have thought worth trying.

Insufficiency

The second ground on which Biogen's patent was attacked was that of insufficiency. An invention will be declared invalid if 'the specification does not disclose the invention clearly or completely enough for it to be performed by a person skilled in the art'[7].

How far the specification must go in providing information and instructions relating to the invention has been a matter of some discussion. However, it is clear that the specification does not have to be complete in every detail, so that anyone whether skilled or not, can perform it[8]. But what is the minimum disclosure required?

Judge Aldous, in the High Court, had applied the 'one-way' rule, as expounded by the EPO Board of Appeal in Genentech I/Polypeptide Expression[9]. In that case, the patentee had invented a plasmid suitable for transforming a bacterial host. This plasmid included an expression control sequence to enable the expression of foreign DNA as a recoverable polypeptide. Initially, the EPO were only willing to grant a patent in respect of plasmids, bacteria and polypeptides that were known as at the date of the application. However, the Board of Appeal ruled:

> an invention is sufficiently disclosed if at least one way is clearly indicated enabling the skilled person to carry out the invention.

Judge Aldous found that Professor Murray's method had produced both antigens in *E. coli*, and that expression would also be achievable in other hosts. Therefore, the Judge found the patent not to be insufficient.

On the other hand, the Court of Appeal in Biogen v. Medeva preferred the reasoning advanced in the case of Exxon/Fuel Oils[10]. In that case, the applicant was appealing against an EPO decision to refuse to grant a patent relating to a method of treating fuel oils to give them better low-temperature handling characteristics, and the Board of Appeal said:

> the disclosure of one way of performing the invention is only sufficient within the meaning of [the sufficiency requirement] if it allows the person skilled in the art to perform the invention in the whole range that is claimed.

The Court of Appeal in Biogen v. Medeva decided, in effect, that there were four separate inventions – expression of both core and surface antigens in bacterial and non-bacterial hosts, and that Professor Murray had only expressed core antigen in bacteria. Therefore, the patent was insufficient.

The House of Lords took a different tack. Their Lordships had previously redefined the inventive concept and went on to describe the minimum disclosure required for sufficiency as an 'enabling disclosure'. However, the House of Lords thought that the meaning of 'enabling disclosure' was unclear and consequently went on to revisit various relevant cases.

The House of Lords noted that in Genentech I/ Polypeptide Expression[9] (the case that gave rise to the 'one-way' rule followed by Judge Aldous in the Biogen v. Medeva case), the EPO Technical Board of Appeal had also said that:

> the character of the invention this time is one of general methodology which is purely applicable with any starting material and is, as it was already stated, also independent from the known, trivial or inventive character of the end-products.

Thus, the House of Lords reasoned, the applicants in that case had invented a general principle for enabling plasmids to control the expression of polypeptides in bacteria and there was no reason to believe it would not work equally well in any plasmid, bacterium or polypeptide. The patent was therefore granted in general terms.

The House of Lords therefore thought that the case had been misinterpreted and the 'one way' rule was too general. The specification must still enable the invention to be performed to the full extent of the monopoly claimed. If the invention discloses a principle capable of general application, then the claims may be in correspondingly general terms, and the patentee need not show that he has proved his application in every individual instance. On the other hand, if the claims include a number of discrete methods or products, the patentee must enable the invention to be performed in respect of each of them.

This can be illustrated by way of patents for pharmaceutical products. If the patentee has hit upon a new product that has a beneficial effect, but cannot demonstrate that there is a common principle by which that effect will be shared by other products in the same class, he is entitled to a patent only for that particular product but not for the whole class (even if, subsequently, other members of the class have the same beneficial effect). On the other hand, if the patentee has disclosed a beneficial property that is common to the class, then 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.

The House of Lords in Biogen v. Medeva then went on to approve a passage from Exxon/Fuel Oils[10] (the case referred to by the Court of Appeal):

> [the requirement] that the claims must be supported by the description ... reflects the general legal principle that the extent of the patent monopoly, as defined by the claims, should correspond to the *technical contribution* to the art in order for it to be supported, or justified (emphasis added by the House of Lords).

Applying these principles to the Biogen v. Medeva case, the House of Lords first considered the technical contribution to the art which Professor Murray made in 1978. It was accepted that Professor Murray had shown that known recombinant techniques could be used to make HBV antigens in bacterial hosts (in spite of the uncertainties that then existed over whether the HBV DNA had introns and doubts as to whether eukaryotic DNA could generally be expressed in bacteria). Professor Murray had found one method of making antigens, but once the sequence of HBV genomic DNA was known and found not to contain any introns, then no one would subsequently use Professor Murray's particular method, as disclosed by the patent. For instance, later researchers may excise the antigen genes from the HBV DNA differently (using known restriction sites) and express the antigen in a different (possibly non-bacterial) host.

Nor, the House of Lords decided, would such researchers be making use of any general principle disclosed by the patent. The inventive concept, as redefined, was 'the idea of trying to express *unsequenced* eukaryotic DNA in a *prokaryotic* [i.e. bacterial] host'. However, the patent actually claimed a monopoly to *any* recombinant method of making HBV antigens in *any* host. The House of Lords decided that Professor Murray's technical contribution, brilliant though it was, did not justify such a wide claim. The patent was therefore found to be insufficient.

Implications of the House of Lords' decision

The disapproval by the House of Lords of the Court of Appeal's interpretation of obviousness could be considered favourable for patentees generally. Most inventions are made as a result of commercial decisions and these are no longer considered relevant. In addition, the use of known techniques to achieve a known goal (a difficulty for biotechnology patentees) will not necessarily be considered obvious. An invention can be patentable as long as the method of obtaining the goal was itself a non-obvious choice.

However, a patent must not claim an invention that goes beyond the inventor's technical contribution to the art. In this case, by narrowing the ambit of the inventive concept, the House of Lords was content to assume that the patent was non-obvious, but then went on to conclude that the patent claims were too broad, i.e. they went beyond Professor Murray's contribution to the art and what was disclosed in the patent specification.

On the other hand, broad claims will now require a correspondingly broad or general disclosure. This may give rise to difficulty in the case of existing patents, which may be phrased to include expression in 'all suitable hosts'. In Biogen v. Medeva, the House of Lords held expression in a eukaryotic host to be outside the inventive concept. Thus, patents that include expression in hosts which have not strictly been enabled (because, for instance, the use of such hosts was unknown at the date of application) may be invalid for insufficiency.

One must, however, contrast the situation where the expression of that particular DNA was not a goal shared by others in the field. If it was not a known goal, then the inventive concept would have been the goal or general principle of expression of HBV antigens. The disclosure need then have only enabled one particular way of expressing that DNA and the patent could be held valid. A possible example appears in a recent case decided by the English Court of Appeal (Chiron v. Organon)[11]. In that case, Chiron's patent covered the expression of Hepatitis C antigens and their use. The Court of Appeal agreed that the patent was valid, at least partly because Chiron had been the first to identify the virus, sequence its DNA and establish an antibody–antigen response.

The decision of the House of Lords in Biogen v. Medeva confirms that patent protection for biotechnology inventions is and will be available in the UK provided the scope of the monopoly claimed is commensurate with the disclosure to the public.

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In short...

In a new series of yearbooks published by **Datamonitor** (New York, USA) it is predicted that more than 75% of market share of the top 25 selling drugs will reside with five companies by the year 2005. As a result of **Pfizer**'s strong pipeline, it will become second only to **Glaxo Wellcome** (18.6% vs. 23.9%). The other companies are **Merck** (18.1%), **Johnson & Johnson** (7.3%) and **Novartis** (7.2%).

Neurex Corporation and **Warner-Lambert** have announced their intention to initiate the Phase III clinical program for the calcium channel blocker SNX111 in the treatment of head trauma. The first study will include 40 centers and 800 patients.