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Patenting in Biotechnology: the Saga Continues

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Introduction

Before the advent of biotechnology, patent law was considered by many to be a relatively dull subject. Although chemical inventions, especially in the pharmaceutical field, had thrown up some interesting questions for patent law, touching on the two primary concepts of novelty and inventiveness (non-obviousness), it was biotechnology that really brought the patent law to life. Another common view, which biotechnology changed, was that patents were appropriate for industry but not for scientists in academic institutions. Again, patent law was often said to have become too complex – 'more complex than the quantum theory' as one biological scientist remarked – and in need of simplification. A defence to this particular charge is that patent law becomes complex mainly by having to respond to the ever-increasing complexity of technology, and this is certainly true for biotechnology patenting. One can also add that it is the ingenuity and audacity of some would-be patenters which raise such difficult problems for the legal authorities such as, for example, the attempt to patent DNA sequences either before actually making them or before establishing any genuine use for them.

CONTENT OF PREVIOUS REVIEWS

Previous reviews of this subject (Crespi, 1985,1989,1993) have attempted to show how patent law has had to accommodate inventions in the biological sciences in a framework which many suggest has been devised primarily for mechanical and electrical engineering inventions and for inanimate chemical compounds and processes. These will be referred to as Reviews 1,2,3, as appropriate.

Review 1 gave a basic introduction to the law and its historical development leading up to what were the chief topical issues at that time, relating to the patenting of microbiological processes and products, especially the patenting of micro-organisms *per se*. Review 2 reported on the beginnings of UK and US litigation on patents for inventions in recombinant DNA and monoclonal antibody technologies. It also

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introduced the subject of legal protection in the field of plant biotechnology and the problem of interface between patents and plant breeders' rights, which was coming into prominence for resolution by official patent circles both national and international. These included the studies carried out for the World Intellectual Property Organization (WIPO) in Geneva and the proposal by the European Commission in Brussels for an EC Directive on the Legal Protection of Biotechnological Inventions.

Review 3 showed how the patentability requirements of novelty and inventiveness were being interpreted in the courts and tribunals of the UK, USA, and of the European Patent Office. The controversial issue of patenting partial gene sequences (expressed sequence tags) was also critically discussed. This had generated much heat in both the patent and academic fraternities at that time and threatened to present a major challenge to the credibility and acceptability of the patent system in the eyes of those involved in important biotechnology programs including the Human Genome Organisation. Review 3 introduced the ethical questions arising from the patenting of plants, animals, and human tissue or tissue-derived materials which were being raised as contentious issues by groups variously concerned with matters of ecology, animal rights and welfare, and as part of a general ideology which is hostile to most aspects of modern biotechnology. The proposed EC Directive, outlined in Review 3, came to be a very convenient forum for this kind of opposition, which various parties influential in the European Parliament were soon to exploit to the full, as will be reported below.

It is timely to present a further chapter in this continuing saga. To minimise the inconvenience of repeated reference back to the earlier reviews, some recapitulation of previous points and examples will be necessary to make this contribution as self-contained as possible.

Patenting of DNA and DNA-derived products

The most high-profile of the topics to be covered in the present review is that of the patenting of genes, especially human genes, and human materials in general. Legal experts have reviewed this subject comprehensively (e.g. Straus, 1996) from the viewpoint of legal policy and have defended the present official practice of allowing genes to be patented if they fulfil patentability requirements.

The US, European, and Japanese Patent Offices have declared their joint agreement to the patenting of purified natural products in appropriate circumstances (USPTO, EPO, JPO, 1988). Their statement did not refer specifically to gene patenting but the reasons given for justifying their practice must apply also to genes. The opposition to gene patents is the current expression of the more general objection to 'patenting life' and 'commodifying life' which are still the favoured slogans of the opposing camps. It will be necessary later to discuss the objections that are being raised against the patenting of DNA sequences and the answers that may be given to these objections. Before addressing these aspects it will be helpful to remind the reader of some of the important case law discussed previously and to review more recent developments.

As a preliminary it must be asked how genes and other DNA materials can be categorized as 'inventions' and whether the methods used for isolating them can be regarded as 'inventive' for the purposes of patent law.

THE CONCEPT OF INVENTION AS APPLIED TO GENES

Patents are designed to protect 'inventions' and not other types of achievement, however meritorious. But the criteria for defining an 'invention' cannot be easily formulated and one has therefore to use specific cases decided by the courts over many years as signposts for future application. Review 3 compared some of the biotechnology case law in UK, USA, and in the EPO in the hope of determining an emerging pattern. This has to be monitored continually because the pattern is likely to change as new questions arise and the courts become more familiar with this technology. Unfortunately, as these three jurisdictions are now showing differences of approach, the matter is not getting easier.

Because a patent conveys an exclusive right, it is clear that the notion of a patentable 'invention' is not to be equated with experimental skill or achievement, as such, since no-one can possibly expect to monopolise abilities of this kind. Also, to justify a patent, something more is needed than simply being the first to achieve something. For example, the sequencing of a gene is not itself sufficient basis for a patent. Analytical work of this kind might be viewed as discovery rather than invention. But where sequencing is part of a more comprehensive achievement which includes identification, isolation, cloning, and expression, and something of practical utility results for the first time from all of this, the achievement is seen by the official patent authorities as going beyond mere discovery and into the realm of invention. This is an answer to those who try to discount gene patents by using the 'mere discovery' argument.

Nevertheless, it is often difficult to define precisely in what the 'invention' consists. Some of the first recombinant DNA inventions to come before the courts have undoubtedly involved a massive experimental effort which justifies the applause of the scientific community. However, patentability has to focus on the inspiration rather than the perspiration and this is not always easily pin-pointed in the patent claim. Thus a claim to 'a DNA sequence coding for polypeptide X' simply states the result without conveying the 'inventive step' that was involved in producing it.

The law states that inventiveness is lacking if what was done was 'obvious' to a person of ordinary skill in the art. To express the opposite of 'inventiveness', patent law has been unable to find an alternative to the highly pejorative term 'obviousness' when considering whether a patent should be sustained or invalidated. The term has very little to do with the assessment of scientific merit but it unfortunately conveys the impression that the court is judging the achievement as something trivial. This is not so. The misunderstanding arises from the fact that patent law is tied to its origin as a legal scheme for the recognition of 'invention', which is not necessarily the same thing as the activity that science judges most worthy, namely, the application of first-class scientific logic and experimental skill. This difference of approach can perhaps be better understood, when looking at a particular patent, by asking first 'was this the obvious thing to do?' and then, 'was it all straightforward?'.

With the foregoing question in mind, it has to be recognized that the conventional style in which scientists write scientific papers or present proposals for research grants is often rather different from the way in which patents have to be written. Scientific papers usually describe the research as following lines of logical progression from previous work and they avoid any hint of sensationalism. Likewise, grant proposals will often stress the likelihood of producing successful results based on what is

reasonably predictable. But for reasons explained above, patents tend to lay stress, wherever possible, on the unexpected and even surprising nature of what the research has discovered. This accounts for them being written in the familiar 'eureka' style. This reviewer will refrain from taking sides as to which mode of writing conforms to actual reality in most cases.

OBVIOUSNESS AND THE RELEVANCE OF 'PRIORITY DATE'

Whether something is inventive or obvious is a matter always to be judged at a particular date. In Review 3, the discussion of the ASAHI case in the UK courts explained the concept of 'priority date'. As this aspect of the law has been crucial to the outcome of some of the cases to be discussed below it is proposed to recapitulate the relevant principles. This kind of procedural detail may not be compulsive reading for the scientist but perseverance will help to make sense of the decisions being handed down by the courts.

Priority date is a factor which arises in two ways. The first and obvious situation, which will be dealt with more fully later, is where two or more inventors are independently applying to patent the same invention and there is a contest as to priority. The second situation, which is more pertinent to the present discussion of obviousness (and even more importantly to the question of novelty), is where public disclosures take place in the literature or elsewhere which are relevant to the novelty or inventiveness of what is being claimed in the patent or application.

The term 'disclosure' has been used above in preference to 'publication' because for most scientists 'publication' means literature publication. For patent law, publication covers all disclosures other than those under strict secrecy and confidentiality. For example, it includes theses available in a University library, pre-circulated abstracts, posters and oral disclosures at public scientific meetings (even those made during the coffee break) if they are made without reservation.

There continues to be a significant difference in the way priority questions and the legal effect of public disclosures are dealt with under US patent law and under the laws of most other countries, although there are factors common to all such laws. The following remarks apply mainly to the non-US situation.

The filing of a patent application gives the applicant a priority date for whatever the application discloses. Relevant public disclosures by third parties, or even by the applicant himself, which occur before the priority date are considered 'prior art' which may deprive the application of novelty or inventiveness. If the date of these disclosures, i.e. when the information is actually made available in any way whatever, is on or after the priority date, they are not counted as prior art.

As explained in the very first of these reviews (see text and diagram on pages 19/20 of Review 1) a patent application can itself be allowed to go through the official examination procedure of the patent office or it may be used solely as a base for claiming priority in a further patent application (the final application) filed within twelve months from the first. This provision was introduced into international patent law in 1883 (the Paris Convention) to allow inventors to start the patenting process at low cost in their home country and to postpone for one year the cost of extending it to foreign countries, whilst retaining the priority date of the original filing.

This facility is illustrated in the graphical scheme (*Figure 1*).

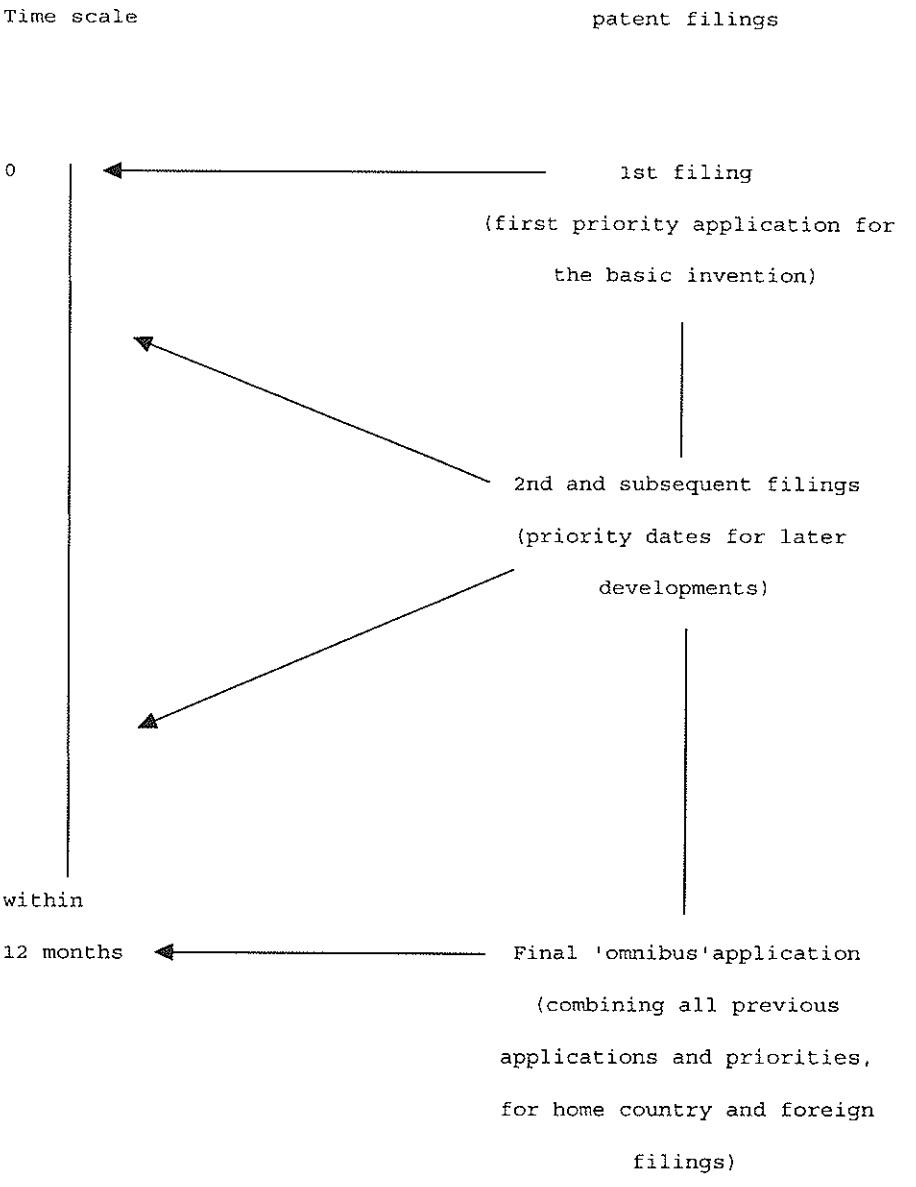

Figure 1.

Applications filed after the first application can update the original disclosure and even add to it significantly. This facility can used to combine a series of successive patent applications, filed within a one-year span and describing developments of the original invention, into one final 'omnibus' application, which will usually contain a number of claims of varying scope. The priority date which attaches to any one of the various claims in the final application is that of the particular previous application which 'supports' it by clearly disclosing the relevant subject matter. Where any

pertinent publication in the literature (or any other kind of disclosure) intervenes during this one year period, it will be crucial to be able to claim a priority date earlier than the publication date.

Examples of the application of these principles, given in Review 3, were the ASAHI case and the BIOGEN alpha-interferon case. These can be summarized as follows.

THE ASAHI CASE

In the ASAHI case, claims to certain DNA sequences were held entitled to the priority of the application that supported them by having the proper 'enabling disclosure' i.e. the application that not only identified each sequence but also described the preparation of the substance itself. By having the necessary supporting disclosure, the Asahi application was accorded an earlier priority than that of another application (Dainippon's) filed earlier than Asahi's but lacking preparative detail and therefore lacking the required 'support'.

THE BIOGEN ALPHA INTERFERON CASE

In this case, the final application claimed priorities from the first and two subsequent applications (called Biogen 1, 2, and 3). The final claims were held not entitled to the priority of Biogen 1 and, consequently, the inventors' scientific paper containing the Biogen 1 data, which was published soon after the filing of Biogen 1, was considered by the EPO to be prior art damaging to inventiveness. The Technical Board of Appeal reversed the EPO Examining Division on this point of law but was itself then reversed by the Enlarged Board of Appeal, so restoring the original judgement.

Disasters of this kind can be avoided by postponing all scientific publication until after the final patent application has been filed, but such delays are usually unacceptable to the academically minded researcher. The problem would be much reduced and might largely disappear if European law were to adopt a one year grace period for the inventor's own publications, such as provided in the US law, which seems to work well and to disadvantage nobody.

PRIORITY UNDER US PATENT LAW

The above summary has to be modified in some respects for the corresponding US law. Priority in US law is decided by determining who is the 'first-to-invent' (rather than simply the 'first-to-file') and this depends on having laboratory or other factual documentary evidence of inventive activity before filing any patent application. At the time of the last review, US law considered such evidence only if lodged in the US. So the foreign inventor could not rely on notebook records in his home country in a contest with a resident US inventor. The US law has now changed to give equal treatment to resident and non-resident inventors, but it must be noted that the rules for recording notebook evidence are rather exacting and must be adhered to if the notebooks are to be relied on (see later).

Invention in US law is seen as a two-stage process involving 'conception' of the invention and then 'reduction to practice'. These factors figure in the priority contest between 'rival' US patent applications or patents, known as 'interference'. How these

matters are decided in particular cases has become so specialized a branch of the law that any attempt to present a simple summary would be inadvisable.

For US law the term 'invention date' is more often used than 'priority date'. By establishing an invention date the inventor can 'swear back of' certain otherwise damaging publications (only those dated within one year prior to the US patent application date). Also, the inventor's own publications are not damaging if dated within the year prior to filing the US application. These provisions avoid many of the problems that can arise under, say, European patent law over the matters of priority date and intervening publications mentioned above.

In the Hybritec sandwich assay case using monoclonal antibodies (outlined in Reviews 1 and 2) conception was defined as 'the formation in the mind of the inventor of a definite and permanent idea of the complete and operative invention, as it is hereafter to be applied in practice'.

Reduction to practice means physically making or performing the invention.

In the contest for priority as between two applicants claiming the same invention in the US Patent Office (Interference proceedings) the matter is resolved by the balancing of three factors, date of conception, date of reduction to practice, and whether there was diligence in progressing from the first to the second.

THE ERYTHROPOIETIN CASE

The erythropoietin case (Amgen v Chugai, 1989, 1991) discussed in Review 3, was not an interference proceeding, as such, but it gave the US court the occasion to apply these considerations to a gene patent. Erythropoietin is the natural protein which stimulates the production of red blood cells and it has considerable utility in the treatment of anaemias and other blood disorders. Amgen holds US Patent 4 703 008 for the preparation of erythropoietin by recombinant methods. However, the claims of the Amgen patent are directed to 'a purified and isolated DNA sequence' encoding the protein, and to the corresponding vectors and transformed cells. For reasons to be explained later, the recombinant epo product is not claimed as such and there is no claim to a process for making it by this method.

In relation to the purified isolated epo gene, the priority of the Amgen inventor Fu-Kuen Lin over others working in this field, especially Edward Fritsch, consultant to Genetics Institute, came under challenge in this case.

The Court of Appeal for the Federal Circuit (CAFC) said:

> A gene is a chemical compound, albeit a complex one, and it is well established in our law that conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials, and to describe how to obtain it . . . Conception does not occur unless one has a mental picture of the structure of the chemical, or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it. It is not sufficient to define it solely by its principal biological property, e.g. encoding human erythropoietin, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property. We hold that when an inventor is unable to envision the detailed constitution of a gene so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, i.e. until after the gene has been isolated.

The court decided that Lin was the first to achieve this. Fritsch had not yet arrived at the claimed invention because 'all he had was an objective to make an invention which he could not then adequately describe or define' and because 'Conception of a generalized approach for screening a DNA library that might be used to identify and clone the epo gene of then unknown constitution . . .' was not conception of the claimed invention.

The court held that in this case the isolation and identification of the gene by the Amgen inventor amounted to a simultaneous conception and reduction to practice of the invention.

THE FIBROBLAST BETA INTERFERON CASE

The CAFC had a further opportunity to develop these ideas in an Interference (Fiers v Sugano, 1993) between three US patent applications claiming

> A DNA which consists essentially of a DNA which codes for a human fibroblast interferon beta polypeptide.

This was an interference between three applicants none of whom was a US resident worker, which meant that the contest was based primarily on their respective priority patent filings in other countries, Sugano in Japan, Fiers in UK, and Revel *et al.* in Israel.

Sugano's Japanese application in March 1980 had disclosed the complete nucleotide sequence of the gene. The Revel *et al.* Israeli application in November 1979 had disclosed a method for isolating a fragment of the DNA coding for beta-IF, as well as a method for isolating beta-IF mRNA, but did not disclose the complete DNA coding sequence. Fiers was the last to file, in April 1980, but he argued for an earlier date based on his disclosure to two US scientists who, on returning home, effectively introduced the concept into the US.

The CAFC supported the Board of Appeals in awarding priority to Sugano because his was the first document to show the full sequence and a method for obtaining it. Confirming their own holding in the Amgen case the court said that 'conception of a DNA, like conception of any chemical substance, requires a definition of that substance other than by its functional utility'.

It also held that:

> Conception of a substance claimed *per se*, without reference to a process, requires conception of its structure, name, formula, or definitive chemical or physical properties.

In laying down this rule, the court declared that to allow a patent based only upon an idea and a hoped-for function would encourage inventors to file speculative applications for patents before they had made their inventions. In a later part of their judgement, touching on the fact that the claim covered all DNAs that code for beta-IF, the court remarked in memorable terms that 'claiming all DNAs that achieve a result without defining what means will do so is an attempt to pre-empt the future before it has arrived'.

The CAFC has therefore now made quite clear what is required for an adequate (enabling) disclosure in the area of gene patents. These cases have been settled in the

context of parallel competing patent applications where the question of first inventorship is in issue, and they have the merit of fairness and plain sense in this situation. However, it is not entirely clear to this reviewer why the principles do not also apply to the form of claims allowed to the winner of the contest which, in both the erythropoietin and beta interferon cases, are not restricted to specific sequences but are broad claims to 'DNA plus function'.

PROVING INVENTION DATE UNDER THE NEW US LAW

In order to prove an invention date for interference and other US purposes, laboratory note book records previously counted as evidence only for actions done in the US. This favoured the resident US inventor as against the foreign inventor. As a result of the conclusion of the Uruguay round of the General Agreement on Tariffs and Trade (GATT) and the related agreement on Trade-Related Aspects of Intellectual Property (TRIPS), the US law has now changed to give equality to foreign laboratory records, if made in the proper manner. This change became effective on January 1, 1996. The manner of making acceptable notebook entries for this purpose is formal and exacting. A brief pamphlet outlining the rules has been published (BTG, London) and a book is also available (H.Kanare, American Chemical Society).

Patent sufficiency and support

A patent can be conceived in terms of a 'bargain' between an inventor and the public. Rather than using an invention as an exclusive secret, the inventor discloses the invention for the public benefit. In return for this gesture, the inventor is protected for a limited time against copying by others. When this time comes to an end, use of the invention is free for all. It follows that there must be some correlation between the extent of the inventor's patent disclosure and the scope of the inventor's patent protection. When the patent application is officially examined, sufficiency of disclosure is a critical issue considered by the patent Examiner, along with those of novelty and inventiveness.

There are two related problems that pre-occupy the patent courts and officials at the present time. First is the problem of assessing the effectiveness of the patent description (based on data provided by an inventor) to enable the skilled person to perform the invention (the 'enabling disclosure'). Second is the question whether the patent description 'supports' the claims of the patent. In Europe these two criteria are dealt with as separate Articles both in the European patent convention (EPC) and in the national patent laws of individual countries.

Why these points were seen as separate requirements when the EPC was created has previously not been at all clear and this has given rise to some difficulty in the courts, as will be explained later. In his own sphere, the research scientist can well understand the distinction between a paper which provides enough information to enable the author's results to be reproduced by his peers and one which provides enough data to support the author's conclusions. But for European patent law, sufficiency and support are now coming to be considered as two sides of the same coin, since both have to be assessed in relation to the patent claims, which determine the scope of the legal protection. Both investigations converge on the patent description which has to teach

the skilled person how to put the invention to use. What the inventor has actually done in the laboratory is, in a sense, less important than the ability to write a recipe for others to follow.

SCOPE OF CLAIMS IN US LAW

US patent law deals with the question of claim scope through the Section 112 of the patent statute and its interpretation through case law. Thus it has been held that 'the enabling disclosure of the specification must be commensurate in scope with the claim'. (In re Hyatt, 1983).

In spite of the Hyatt dictum, many very broad claims have been allowed in recent US biotechnology patents and their pre-emptive effect has been the subject of concern. Some who have been the first to produce a particular type of recombinant product or transgenic plant have sought to dominate all ways of making such products by obtaining *per se* claims (to the product or the DNA encoding it) of the broad functional type, usually unrestricted as to nucleotide sequence. This strategy failed in the Tissue Plasminogen Activator case (UK) on grounds of the 'obviousness' of the method used but succeeded in the Erythropoietin case (US) in view of the original method of isolating the gene. Patent protection is normally justified on the basis that the patent provides a new 'teaching' which others require if they are to succeed. In some biotechnology patents this is lacking – the claim of first achievement seems to be a substitute for such a teaching.

The two outstanding examples of transgenic plant patent which have attracted comment in relation to their breadth are:

- US 5 159 135 which has claims broad enough to cover any transgenic cotton plant or seed which contains a foreign gene which will express a foreign protein or negative strand RNA, and
- European patent 301 749 which claims a soybean seed having a (i.e. any) foreign gene which expresses a foreign gene product in the plant cells.

The descriptions in both these patents describe one special way in which the gene has to be inserted – for cotton, insertion into hypocotyl tissue, and, for soybean, by bombardment with accelerated plasmid particles – but the broadest claims directed to the plant or seed cover all ways of producing the product.

These are not the first patents of such wide scope. For example, the Hibberd case mentioned in Review 1 claimed ' A maize seed having an endogenous free tryptophan content of at least about 1/10 mg per g. . .' and this was allowed without challenge to its scope.

The following US case shows a much tougher line being applied.

LIVE VACCINES AGAINST RNA VIRUSES (IN RE WRIGHT, 1993)

The claims in this US patent application were directed to live vaccines for pathogenic RNA viruses. The specification provided a general description of the processes of making them, and methods of use, but only a single working example, namely, a recombinant vaccine against Prague Avian Sarcoma virus (PrASV). The example

showed the cloning of a part of the envelope gene region and transfection into a chick embryo cell line. The broadest product claim was:

> A live non-pathogenic vaccine for a pathogenic RNA virus, comprising an immunologically effective amount of a viral antigenic expression (product) having an antigenic determinant region of the RNA virus, but no pathogenic properties.

The equally broad process claim covered the steps of 'identifying the antigenic and pathogenic regions of the virus, performing gene alteration to produce a genome which codes for the antigenicity of the virus but does not have its pathogenicity, and obtaining an expression of the gene'.

Claims of this kind seem to this commentator to be little more than a generalized statement of what anyone would know had to be done to produce a vaccine, even as early as February 1983 (the priority application date). This type of claiming seems to be typical of many such recombinant DNA patents.

The Examiner had allowed claims specific to the exemplified avian virus but took the position that the broad claims required to be supported by a disclosure which would enable the skilled person to produce vaccines against all RNA viruses, so that 'undue experimentation' would not be required to apply the methodology of the single given example to other members of this diverse range of viruses.

The Board of Appeal sided with the Examiner and further held that no evidence had been given to establish that the immune response produced by the envelope protein was immunoprotective.

Supporting both the Examiner and the Board, the CAFC, hearing the case in July 1993, pointed out that if the Patent Office make this type of objection, they have the burden of showing that it is a reasonable one. Here the Examiner had pointed out that the claims were broad enough to cover a vaccine against AIDS and she had cited literature showing how difficult it would be to produce such a vaccine. The applicant had filed supporting affidavits by scientific colleagues but these contained only unsupported statements as to the legal question and were not convincing. The CAFC held that the evidence failed to show 'that, in February 1983, a skilled scientist would have believed reasonably that success with a particular strain of avian RNA virus could be extrapolated with a reasonable expectation of success to other avian viruses'.

It follows from this that not even a limitation to avian viruses would have succeeded in this case.

SCOPE OF CLAIMS IN EPC LAW

EPC deals with this issue through Article 83 (sufficiency) and Article 84 (support). The leading case T292/85 (GENENTECH/Polypeptide Expression 1985) concerned one of the earliest applications in the field of genetic engineering.

THE GENENTECH CASE T292/85 (GENENTECH 1989)

The main claim was directed to a recombinant plasmid defined in terms of certain structural and functional features, including the presence of a homologous regulon and a heterologous DNA coding for a desired polypeptide and in proper reading frame.

The Examining Division had objected to the use of the broad 'bacteria, regulon, plasmid etc', arguing that these should be limited to specified known materials in order to meet the requirement of sufficiency and to avoid covering future discovery of new materials falling within these broad descriptions.

The Technical Board of Appeals held that subsequently-discovered variants could be legitimately covered if they achieved the same effect 'which could not have been envisaged without the invention' and they also held that the Examining Division's argument had no support in the EPC.

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

This case has often been quoted as holding that sufficiency is met by disclosing 'one way' of carrying out the invention. This view not only ignores the qualification 'at least' but also ignores the whole context of the decision which, in this reviewer's opinion, does not justify claims of totally unlimited scope such as in the cotton and soybean patents noted above. In any event, the T292/85 quotation has been put into proper context by a later case outlined below.

THE EXXON/FUEL OIL CASE T409/91 (EXXON 1994)

In the Exxon case the invention lay in the use of certain additives to fuel oil to inhibit the growth of wax crystals which would plug the filters. The claim did not recite the presence of the additives but merely specified wax crystals less than 4000 nanometres. Since the need for small crystals to avoid the problem was already known in the art, the Technical Appeal Board held that the claim lacked the necessary reference to the particular technical solution provided by the invention i.e. the specific additives. For this reason the claim did not meet the requirement of Article 84.

The Board described the claim as 'an attempt to cover not only the technical contribution to the art actually described but also to monopolise a technical area extending well beyond it'. It went on to distinguish from the genentec T292/85 case on the related question of sufficiency of description and held that 'the disclosure of the claimed invention is only sufficient if it enables the skilled person to obtain substantially all embodiments falling within the ambit of the claim'.

This reviewer considers this 'all embodiments' test to be a very demanding one which moves to the other extreme from that of the 'one-way' test indicated above. One difficulty in applying it is that it can rarely be clear to an Examiner that the description given by the inventor will fulfil the test. The Appeal Board could simply have qualified the admittedly inappropriate 'one-way' test without imposing another test of an equally unrealistic kind.

Some recent legal decisions on DNA patents

The legal issues referred to above have been tackled in recent EPO and national court decisions on some commercially important recombinant DNA patents. These deserve summary because of the light they shed on the subject. The cases are also of interest in that they show divergences of approach toward the same patents, as between the

EPO and the national courts (specifically the British courts). European patents are granted by the EPO but within 9 months from grant they can be formally opposed by third parties. The Opposition proceedings are handled by the EPO and the Appeal Boards, which can either support, amend, or revoke the patent as appropriate. After that period, assuming a patent survives an Opposition or if no Opposition has been entered, the patent falls under the jurisdiction of the courts of each country designated in the EPC patent application.

National courts show considerable respect for the judicial decisions of the Boards of Appeal of the European Patent Office. National courts also consider that harmonious international development of patent jurisprudence is a highly desirable objective. Nevertheless, patent litigation in national courts is largely dictated by the litigants and may take a different course from that followed in EPO proceedings. Thus the investigation of patent validity in revocation proceedings may go deeper in the national jurisdiction e.g in the exploration of expert evidence and the power of the court to appoint its own scientific advisers. Cases in national courts also last for a much longer time.

The English courts were the first to revoke a recombinant DNA patent obtained under a national route. This was the patent for recombinant tissue plasminogen activator on which Genentech sued the Wellcome Foundation for infringement and Wellcome counterclaimed for revocation (see Review 1). A summary of the UK litigation will be given here for comparison with the decision of the Technical Appeal Board on the corresponding European patent application.

GENENTECH'S UK PATENT 2 119 804 ON TISSUE PLASMINOGEN ACTIVATOR (T-PA)

The principal claims in this patent were product claims directed to the recombinant product, as in the following claim:

> Human tissue plasminogen activator as produced by recombinant DNA technology.

This claim covers human t-PA prepared by any recombinant DNA technique and it is a product-by-process claim of broad scope. The claim would appear to cover only the recombinant version of the natural product but a much broader interpretation was intended by the patentee, as was made clear from certain 'Definitions' given in the specification. Thus, in addition to allelic variations of t-PA it was stated that all modifications or derivatives of the natural product were to be included, such as those obtained by mutagenesis e.g. having aminoacid deletions, substitutions, additions, or replacements, provided the essential activator function was retained.

THE ENGLISH COURT OF APPEAL JUDGEMENT

The natural t-PA protein was a known substance having been previously isolated from the Bowes melanoma cell line. The amino acid sequence of t-PA had not previously been determined, but one cannot patent a known substance just by being the first to determine its structure. The recombinant product was held obvious by the British court, first because it was a known desirable objective on which a number of groups were working and, secondly, because the court was persuaded that the

product was obtained by using conventional textbook methods of gene cloning.

The court of first instance had said that had Genentech been the first to discover t-PA, its decision would have been different. Since most of the initial applications of this technology have been aimed at producing naturally occurring proteins of known therapeutic value this observation was cold comfort for those using standard techniques in this field. The only consolation that this statement offers is that novel derivatives or analogues of t-PA or other proteins which show some advantage over the natural product cannot be so readily dismissed as unpatentable.

Genentech's British patent was invalidated in late 1988 but, in addition to filing applications in various countries in Europe under their national patent systems, Genentech had also filed a duplicate European patent application, thus providing an alternative route to protection throughout Europe.

THE EUROPEAN PATENT ON T-PA (GENETECH 1992)

The corresponding European patent 93619 issued in September 1989 with a claim structure very different from that of the British patent and relying mainly on process claims, such as,

> A process which comprises preparing cDNA from mRNA extracted from the Bowes melanoma cell line and isolating from it a DNA sequence having the restriction pattern shown in *Figure 4* hereof for the putative mature tissue plasminogen activator sequence and which endcodes a 527 amino-acid polypeptide having human tissue plasminogen activator function.

This was followed by process claims to the expression of the DNA to produce the protein. There were no product claims to the recombinant form of natural t-PA but various related substances were claimed in the following way :

> A protein having human tissue plasminogen activator function and which comprises an allele or derivative by way of amino-acid deletion, substitution, insertion, inversion, addition or replacement of the 527 amino-acid sequence as encoded by the DNA product of claim 1 or 2.

OPPOSITION TO THE EUROPEAN PATENT ON T-PA

Formal Oppositions to this patent were filed by seven Opponents, asserting 35 documents as relevant prior art including a paper in 'Nature' by Pennica *et al.* (the Genentech team themselves). During this Opposition, Genentech had amended their claim by defining the 527 amino-acid sequence specifically 'as depicted in *Figure 5* of the (patent) drawings'. *Figure 5* showed the correct sequence but unfortunately the sequence given in the first UK filing contained three sequencing errors (Lys instead of Glu at position 175, Gly instead of Ser at 178, and Ala instead of Thr at 191). Consequently the Opponents challenged Genentech's right to claim priority from the first UK filing and argued that the earliest date that could be claimed for this purpose was in April 1983. Now the Pennica paper showing the correct sequence had been published in January 1983, so that it would be citable as prior art if the first priority was unsustainable.

The Opposition Division of the EPO considered the sequencing errors to be immaterial in relation to the size of the molecule especially since they did not affect the character of the product. However this decision was reversed on appeal to the Technical Appeal Board. In spite of the fact that the genuine t-PA molecule was produced by the protocol described in the priority document and the sequencing errors would not import any change in biological activity, the Appeal Board insisted that the primary amino-acid sequence was an 'essential characteristic' of the invention claimed and that this had not been correctly disclosed in the priority document.

Consequently the claimed priority date could not be sustained and Pennica *et al* was prejudicial to the patent. Incidentally the German Patent Office had already taken the same strict view of this problem against Genentech's German national application.

The EPO Appeal Board at first commented adversely on the claim to derivatives, which they considered bad for want of a clear definition of the term 'human tissue plasminogen activator function'. They found no less than four definitions of this term in the patent description and could not decide which one was to be taken as crucial. The claim was said to 'relate to a vast catalogue of derivatives of human t-PA of unspecified structure having any unspecified function of human t-PA'. No specific examples of any such derivatives were given in the patent.

However, Genentech saved their patent by proposing amended claims in which the reference to the *Figure 5* sequence was no longer present and which included a definition of 'human t-PA function'. This function was specified in terms of catalyzing the conversion of plasminogen to plasmin, binding to fibrin, and by immunological properties.

As to the broad claim to derivatives, the Opponents pointed out that a wealth of possible derivatives had been claimed but not a single example had been provided. This was 'nothing more than an invitation to carry out a research programme in order to find suitable derivatives. . .'. But, in spite of their original objection to this claim, the Board took the view that, the basic molecular structure of t-PA being given, it would not require inventive skill or undue experimentation to prepare such functional derivatives.

Some commentators argue (Scott-Ram, Roberts, Crespi, 1994, 1995) that the tendency for broad dominating claims to be granted in recombinant DNA patents which 'reach through' to all conceivable second-generation derivatives is bad for the industry as a whole because it is inhibitory to further research. There are however many instances of patents of such breadth and this is the subject of much comment at the present time.

The other notable fact about the European patent decision is its major difference from that of the UK court on the question of inventiveness. On the question whether it was obvious to try to clone the t-PA gene, and whether the methods used were straightforward, the Board held that:

> The various affidavits and declarations of prominent scientists who, on different sides, were involved in this research endeavour confirm that, while there was considerable interest in arriving – possibly before anybody else – at the cloning and expression of human t-PA in a recombinant host, the task was regarded as tough, the prospects of success were considered thin and the announcement of the isolation . . . of a full-length clone encoding human t-PA was received in the interested milieux as a pleasant surprise . . . .

THE BIOGEN/MEDEVA LITIGATION ON HEPATITIS B (BIOGEN, 1995,1997)

This was the first recombinant DNA patent to experience the whole range of English jurisdiction, from the High Court through the Court of Appeal and to the House of Lords.

Biogen/Medeva provides a remarkable example of the uncertainties of the legal process, as explained below. This case required the application of conventional legal principles to a new and technically complex development, occurring at a time when the basic science was in rapid ferment, and against a background of highly pertinent scientific publications of others. Considering the extraordinary demands of comprehension made on the judges, one can only marvel at their grasp of the subject and the lucidity of their respective judgements, even where they disagreed with one another.

THE PATENT IN SUIT

The Biogen patent for the DNA coding for Hepatitis B antigens was a patent obtained under the European Patent Convention (the EPC route) and covering the UK as one of the many designated European States. It is identified as European patent (UK) 182 442. It will be helpful to set out the main claim of the UK patent since the same claim was presented to the EPO Technical Board of Appeal in connection with an Opposition against the European patent itself.

> A recombinant DNA molecule characterized by a DNA sequence coding for a polypeptide or a fragment thereof displaying HBV antigen specificity, said DNA sequence being operatively linked to an expression control sequence in the recombinant DNA molecule and being expressed to produce a polypeptide displaying HBV antigen specificity when a suitable host cell transformed with said recombinant DNA molecule is cultured, the transformed host cell not producing any human serum proteins and any primate serum proteins other than the polypeptide displaying HBV antigen specificity.

Antigen specificity (ability to bind to the relevant antibodies) is the essential criterion of the main claim. The additional property of antigenicity (ability to induce antibodies) is specified in the second patent claim. The claims which follow these were directed respectively to DNA coding for hepatitis B core antigen HBcAg and surface antigen HBsAg. Other claims covered the expression products produced by a host transformed with the claimed recombinant DNA (so-called product-by-process claims).

The European patent application, filed in December 1979, had been preceded by three British priority applications two of which were dated in December 1978 (Biogen I, Biogen II) and the third in November 1979 (Biogen III). In view of publications appearing in the scientific literature over this period by other groups working in this field, the most serious challenge to the patent made by the defendant was one of obviousness. To overcome this it was essential for Biogen to sustain their claim to priority based on the first British filing in December 1978. This meant that Biogen I had to contain a sufficient (enabling) disclosure of the invention claimed in the European patent. Put another way, it was essential for Biogen I to be held to 'support' the relevant claim.

THE MEDEVA COUNTERCLAIM

To develop the insufficiency objection, Medeva argued that the broad main claim covered more than one invention, i.e. that the DNAs coding for core antigen and surface antigen were separate inventions, and that expression in bacterial hosts was a separate invention from expression in eukaryotes. If separate inventions were involved, it would be necessary to assign their respective priority dates. In other words, there would have to be support for them, either in the final patent description (much the same as Biogen III) or in the priority filing, Biogen I.

Medeva had argued that Biogen I supported only one of these inventions, namely, expression of core antigen in *E.coli.* There was therefore insufficient support in Biogen I for the full scope of the 'invention' defined in the main claim of the patent. Medeva also challenged the evidence given in the final patent for expression of surface antigen. This factual point fell to be decided in the light of the evidence disputed among the expert scientific witnesses acting for the parties.

The final patent gave the full sequences for both core and surface antigen but sequencing had been the work of others and published in August 1979. Medeva claimed that the broad claim was not entitled to a priority date earlier than November 1979, and therefore that the 'invention' as claimed was obvious over the August publication as prior art.

This case is a classical example of what can occur in the recombinant DNA field, where papers have already been published which disclose a series of pertinent developments before the patent applicant's own contribution has been made. Medeva relied on four prior publications, including those describing the extraction and partial characterisation of DNA from the causative agent, the Dane particle (November 1975), the purification of proteins from a preparation of the surface antigen and the sequencing of their terminal parts (April 1977), the estimate of the size of the DNA (August 1977), and a 'seminal paper' on the cloning and expression of eukaryotic protein (rat preproinsulin) in *E.coli* (August 1978).

THE TECHNICAL ISSUE OF INTRONS

Throughout this entire case there was much discussion of the question of introns. The point disputed by the scientific expert witnesses was whether or not, at this early date, introns would have been assumed to be present in HBV DNA and, if so, whether this would have made it seem unlikely that the method described in Biogen I (a shot-gun approach) would have succeeded and whether expression could be achieved in *E.coli.*

At this early date, this consideration would doubtless have been relevant to the attempt to express eukaryotic genes in bacteria using vectors known to work in them such as pBR 322. However, the patent explicitly contemplated (without exemplifying) the use of other vectors and other hosts for which, presumably, there would have been less uncertainty over expression. The prior expression of one eukaryotic gene in *E.coli* mentioned above (rat preproinsulin) had been achieved by side-stepping the intron problem by working from messenger RNA to produce cDNA coding for the protein. This strategy would have been impossible to apply in the HBV situation since no mRNA was available. In the final analysis, nothing vital turned on the question of introns.

DECISION OF THE COURT OF FIRST INSTANCE

The High Court judge decided all issues in favour of Biogen, holding that 'the inventive concept was the idea or decision to express a polypeptide displaying HBV antigen specificity in a suitable host'. This was a single over-arching invention covering any species of HBV antigen, whether it be core antigen HBcAg or surface antigen HBsAg. No-one but Biogen had contemplated this at the priority date of Biogen I (December 1978) and Biogen I provided support for this broad concept. However, the judge did hold that, if the December 1978 date had not been allowable as the priority date for the 'invention' as a whole, the claimed subject matter would have been obvious at the date of Biogen III (November 1979) in view of the August 1979 paper describing sequencing of HBsAg.

Before considering the decision of the Court of Appeal, it is desirable to report on the decision of the EPO Technical Board of Appeal on the Opposition to the corresponding European patent.

DECISION OF THE EPO TECHNICAL BOARD OF APPEAL (BIOGEN, 1995)

The Board decided the question of priority date by asking whether the claimed invention was disclosed in the priority document, either expressly or by direct and unambiguous implication. After a detailed analysis of Biogen I, the Board concluded that all the essential elements of the invention were to be found in Biogen I. For the Board it was evidently sufficient that Biogen I indicated that one or more of the known HBV antigens 'could be' expressed, even though no actual demonstration of expression of either HBcAg or HBsAg was provided in the document.

The Board stated that the issue was not one of efficiency of expression, but of expression in general. The Board clearly felt that the burden was on the Opponents to demonstrate that it was impossible to express these antigens to some extent when following the disclosure of Biogen I. The Board seemed to ignore the problem of proving a negative of this kind. The Board decided favourably for the patentee on this point by concluding that the two inventions, as between Biogen I and the patent, were the same. No question as to whether Biogen I 'supported' the claim was apparently entertained by the Board.

The Board considered the question of inventive step along the lines now firmly established in EPC practice, i.e. the problem/solution approach. The problem was stated by the Board to be 'the provision of HBV DNA or fragments thereof in sufficient amounts for the elucidation of its structure and for the production of HBV antigens'. The problem was solved by providing the recombinant DNA molecules defined in the claims.

To this reviewer, it seems difficult fully to reconcile the Board's assessment with what is stated in the patent itself. The problem stated in the patent is two-fold, namely, first, the development of means of detection of the disease and, secondly, one of providing an effective means of infection control and prevention, i.e. a vaccine. The solution is said to be the provision of the claimed molecules which allow the production of HBV antigens in substantial quantities for vaccine preparations and for use in detection of the viral infection. In the light of such assertions, one would have thought that there was indeed a burden on the patentee to show that molecules

resulting from his described method enabled this to be done, even if only at the experimental laboratory stage at which all such inventions originate.

Having concluded that the invention solved the problem, the Board had no difficulty in finding that it was inventive to provide the claimed molecules. It was not significant that other teams were working toward the same end. This fact did not imply that there was a reasonable expectation of success. The latter implied 'the ability . . . to predict . . . a successful conclusion' in an acceptable time scale. The Board distinguished this from 'an understandable hope to succeed'.

THE UK COURT OF APPEAL DECISION

This is best summarised under the following headings:

Scientific advice

This court was assisted in its technical appreciation of the subject by scientific expert advisers, Professors D.Glover and J.Neil, of the Universities of Dundee and Glasgow respectively. The High court had not appointed a scientific expert but the judge had recently heard the Chiron patent case on Hepatitis C, in which he had been advised by Dr S. Brenner (who had previously advised the Court of Appeal in the Genentech/ Wellcome case on tissue plasminogen activator). The experience of the Hepatitis C case must therefore have been still fresh in his mind.

Importance of date

The court remarked first on the central importance of date, noting that the lower court would have found the patent invalid but for Biogen's entitlement to the priority date of Biogen I. The distinction between core and surface antigens and their different uses, respectively, for diagnostic and vaccination purposes was emphasised by the court – indeed the patent itself made this clear by giving the two different polypeptide sequences. The patent had also acknowledged that the expression of HBcAg and HBsAg were separate exercises in the sense that they were not co-produced by the method described in the patent. The court found a serious inconsistency between the claim to provide antigen in substantial quantities for vaccine production and detection of viral infection and the absence of any method of producing HBsAg without knowledge of its sequence (from a publication by others after the date of Biogen I). The sequencing work had also shown that the HBV genes did not contain introns.

The process used

The process used by Biogen was said in the patent to be 'distinguished from prior processes' by their use of natural DNA i.e. genomic DNA. The method consisted in cleaving the natural DNA from the Dane particle into large fragments and using these to transform *E.coli*. Because of the possible (and assumed) presence of introns, which could not be processed by bacteria, this approach was arguably one which would have been considered unlikely to lead to a useful result. It was conceded, however, that the actual methodology used was already known in the art. The invention, their Counsel

said, was 'the realisation to do it' or 'deciding to put the HBV gene into an E.coli expression system'. The High court judge had himself expressed this as 'the idea and decision of using expression to obtain polypeptides' which was 'akin to an invention for a principle'.

The Court of Appeal viewed it another way. What the inventor had done was to try 'a shot-gun experiment, . . . without prior knowledge of the sequencing of the HBV DNA,.. (to see if) . . . any HBV antigen would be expressed in *E.coli*.' This was an experiment which, on the evidence given by expert witnesses to the court below, was thought unlikely to succeed. The Court of Appeal found it difficult to identify this as an invention: 'There was no invention of any principle and no invention of a method of producing anything.' For this court 'a mere commercial decision was not an invention'.

Priority date, sufficiency and support

These questions were intimately bound up with the question of how many inventions were involved. The court insisted that the core and surface antigen polypeptides and their respective recombinant DNA materials were in every respect different products. The term 'HBV antigen' did not connote a single entity but two distinct entities. 'Therefore the questions of priority date, support, inventiveness and sufficiency will have to be considered separately in relation to HBcAg and HBsAg.'

Continuing this theme, the court also decided that solving the problem of expression in non-bacterial hosts, to which the patent made no contribution, was 'inevitably going to be a different invention from that of the plaintiffs'.

On the question of sufficiency of disclosure and claim scope the analysis of this court was similarly devastating. Bearing in mind the developing law of the European Patent Convention, a national court must take account of the relevant EPO Appeal Board decisions on this question. The Court of Appeal did so, and found its views consistent with Technical Board of Appeal decisions in Genentech/Polypeptide Expression T292/85 and Exxon/Fuel Oils T409/91.

The basic question here is whether a patent claim is acceptable which is so worded as to cover a broad range of possibilities when the patent description contains only a single worked example within the range over which it extends. Endorsing the statement in the Exxon decision that the disclosure must be sufficient to enable the whole width of the claimed invention to be performed, the court said:

> The disclosure must be sufficient to enable the whole width of the claimed invention to be performed. What will suffice to satisfy this criterion will vary depending upon the nature of the claim that has been made. It is essential to apply the test having regard to the extent of the claim. It is not the law that the disclosure of a single embodiment will always satisfy the requirement regardless of the width of the claim.

In this case therefore, the disclosure would have to have been wide enough to enable both core and surface antigen to be produced in any host, bacterial or non-bacterial.

Another section of this court's judgement is particularly worthy of quotation because of its aptness to the experience of many patent attorneys (including this reviewer) faced with clients who want to patent ideas which have not yet been reduced to practice:

> An inventor may have an inventive idea and be confident that it will have utility and that means of performing it will be found. However, he may at the time not know how to perform it, nor may the state of the art at that time provide the answer. It therefore will not be possible for his application to include a specification which discloses the invention in a manner which is clear enough and complete enough for the invention to be performed by a person skilled in the art.

This quotation will also be very useful to the patent attorney whose client insists that the invention lies in the idea, as such, and that it would be only a matter of routine to verify it practically (even though he has not done so).

The present case illustrated 'an application to patent products which the applicant did not know how to make and which only subsequently became capable of being made as a result of the later work of others'.

The extent of support in Biogen I

As stated in Biogen I, the invention was based on the discovery that HBV DNA:

> when appropriately cleaved and inserted into a vector such as a bacterial plasmid or phage can be used to transform a host micro-organism so that it produces polypeptides with HBV antigen specificity.

The process then described is all about cleaving the DNA and it is restricted to the use of the well-known plasmid pBR322 and *E.coli*.

Biogen I made little reference to the difference between HBcAg and HBsAg and did not say what antigen specificity was obtained in the shot-gun experiment. As the court observed, it 'offers no principled guidance as to how to obtain a particular result', especially in any non-bacterial host. Therefore the most that Biogen I could support would be a claim to a molecule of DNA which would express HBcAg in a bacterial host.

Obviousness

Having decided that the priority date of Biogen I was unsustainable, and consequently that lack of inventive step was a foregone conclusion, the court nevertheless reviewed the evidence. The court noted that the experiment conducted by the inventor had been assessed at the time by other experts as unlikely to succeed, but it failed to see that to do an experiment with a low chance of success could be equated with an inventive step. The court remarked:

> The distinction between this and an inventive step lies in the difference between some element of novel insight or discovery and a mere business assessment or choice to pursue an identified goal by known means.

Disagreeing with the lower court, the Appeal court felt that 'the plaintiffs did not invent any principle' . . . 'what they did in 1978 was obvious even though no one else chose to do it'.

This decision shows remarkable contrast with that of the Technical Board of Appeal on the corresponding European patent, but that in itself is no reason to dismiss it.

THE HOUSE OF LORDS DECISION

Inventive step

The unanimous judgement of the House was presented by Lord Hoffmann, who began by addressing the problem of identifying the inventive step in a case of this kind. Lord Hoffmann noted that 'The claim was for any recombinant DNA molecule which expressed the genes of any HBV antigen in any host cell' and later that 'The claim was for any method of making a DNA molecule which would achieve the necessary expression.'

But in a statement which fully represents the classical English approach to this type of question he remarked:

> Whenever anything inventive is done for the first time it is the result of the addition of a new idea to the existing stock of knowledge. Sometimes, it is the idea of using established techniques to do something which no-one had previously thought of doing. In that case, the inventive idea will be doing the new thing. Sometimes, it is finding a way of doing something which people had wanted to do but could not think how. The inventive idea would be the way of achieving the goal. In yet other cases, many people may have a general idea of how they might achieve a goal but not know how to solve a particular problem which stands in their way. If someone devises a way of solving the problem, his inventive step will be that solution, but not the goal itself or the general method of achieving it.

Lord Hoffmann rejected both lower courts' assessment of the inventive step. For Lord Hoffmann, 'a more accurate way of stating the inventive step . . . is to say that it was the idea of trying to express unsequenced eukaryotic DNA in a prokaryotic host'. Formulating the inventive step in this way, the argument for inventiveness was 'much stronger'.

Priority date

Lord Hoffmann based his view entirely in accordance with the Asahi case (see above). Thus the question of 'support' and 'enabling disclosure' applied to the description both in the patent itself and, where priority is claimed, in the priority document. Lord Hoffmann reversed the Court of Appeal and held that the views of the High Court and of the EPO Appeal Board in the corresponding EPC patent were to be preferred.

This assessment, Lord Hoffmann felt, was fully in keeping with the principles of Genentech/Polypeptide expression T292/85 and Exxon/Fuel oils T409/91.

The critical issue

But for Lord Hoffmann the critical issue was one which had not been formally raised in either of the decisions of the two lower courts. This was not whether the description could 'deliver the goods across the full width of the patent or priority document' but 'whether the claims cover other ways in which they might be delivered: ways which owe nothing to the teaching of the patent or any principle which it disclosed'.

Based on his own identification of the inventive step, stated above, Lord Hoffmann ruled that:

> The claimed invention is too broad. Its excessive breadth is due, not to the inability of the teaching to produce all the promised results, but to the fact that the same results could be produced by different means.

Concluding his finding on the matter of claim breadth, Lord Hoffmann returned to the question of 'support' and held that Biogen I did not support the invention as claimed in the European patent, which was therefore invalid.

Referring to the EPO Appeal Board decision which sustained the European patent, Lord Hoffmann considered that his crucial point had been missed on this particular aspect of the case. The Appeal Board had concentrated only upon the question of sufficiency in relation to HBsAg and HBcAg, but 'nothing was said about whether the claims were too broad because expression could also be achieved without the use of the teaching which it contained, by a method which could not be said, in the words of the Technical Board in Genentech I, that it was 'in a manner which could not have been envisaged without the invention''. The defendants, who had worked from the knowledge of the HBV genome (the sequence) and had used mammalian host cells, owed nothing to the invention as formulated by Lord Hoffmann. Lord Hoffmann concluded that the principle he had employed to reach his conclusion did not suggest 'any divergence between the jurisprudence of this court and that of the EPO'.

In the specific cases outlined above the question of whether or not the defendant's product fell within the claims i.e infringed the patent was not in serious doubt. The legal dispute concentrated instead on the question of the validity of the patent. In most other fields of technology the defendant will usually deny infringement as well as contesting validity. The topic of patent infringement therefore deserves some explanation.

Patent infringement

The writing of patents for nucleic acids and proteins presents an acute dilemma. One knows that the composition of these molecules may be modified in various ways, leading to mutants, variants and derivative forms which may either retain, enhance or reduce, or totally lose the original biological activity. The patent draftsman attempts to guard against third-party avoidance of claims tied too closely to the limited range of specific products made by the inventors and presented as the patent Examples. But in the absence of data on the effect of compositional variation on activity there is nothing to guide him. The patent Examiners will normally stress the uncertain effect of variation and will insist that the claims are limited to what has been disclosed.

The patent draftsman will usually prepare the ground for a broad interpretation of the claims by the use of a skilfully drawn 'Definitions' section. A comprehensive model of this tactic is to be found in the Human Tissue Plasminogen Activator patents, especially US patent 4 766 075 which is the equivalent of UK patent 2 119 804 discussed above. These definitions of t-PA embrace natural allelic variations and derivatives modified by single or multiple aminoacid substitutions, deletions, additions or replacements in the t-PA molecule so long as the essential biological function of t-PA is retained.

An infringement suit on the US t-PA patents provides an instructive example of how these matters are treated by the courts.

GENENTECH V WELLCOME FOUNDATION AND GENETICS INSTITUTE (1990)

Genentech sued these defendants for infringement of the following three US patents relevant to t-PA:

- 4 752 603 (the '603 patent) is directed to Human plasminogen activator derived from the Bowes melanoma cell line and it covers the original work carried out by Leuven Research and Development. The claims are limited to material of specific activity of 500 000 IU/mg against a specified reference standard. This limitation was necessary because of an earlier publication by one of the inventors describing material purified to an activity of 266 000 units.
- 4 766 075 (the '075 patent) covers 'A DNA isolate consisting essentially of a DNA sequence encoding human tissue plasminogen activator' and the corresponding recombinant expression vectors.
- 4 853 330 covers the process of expressing the DNA of the '075 patent to produce t-PA.

Wellcome's product, made in UK and exported to the US, differed by only one amino-acid from human t-PA, 'the product of the patent'. The Wellcome product (met-t-PA) contained methionine in place of valine at position 245.

The GI product (FE1X) was a product having 81 amino acid deletions from t-PA. It lacked the Finger region and most of the Epidermal Growth region and had other differences in the Kringle region of the native protein.

The District Court of Delaware (in March 1990) held that, on their literal interpretation, the claims in both the '603 and '075 patents were limited to the full-length amino acid sequences of naturally occurring human t-PA and its naturally occurring allelic variants. The court also decided that the specific activity limitation in the '603 patent should also apply to the definition of t-PA in the context of the '075 patent. This was particularly surprising because the claims of the '075 patent were to the DNA coding and not to the protein, either *per se* or at any level of purity.

It being admitted that neither met-t-PA nor FE1X naturally occur in humans and that their specific activities were lower than that specified (or assumed) in the claims, these products were held not to infringe the patent on the literal interpretation. Wellcome also argued successfully that importation of met-t-PA into the US, which involved no use of the claimed DNA or recombinant cell lines in the US, was non-infringing for this reason also.

But US law also has a 'doctrine of equivalents' which the Delaware court described as 'an equitable doctrine permitting a more expansive interpretation of patent claims than the literal scope thereof'. In view of the material issues of law involved, the court declined to rule on this issue and reserved it for further trial. Genentech then applied for a jury trial on the equivalents issue. This commenced 7 days later and resulted within 15 days in verdicts of infringement by equivalents for both products. One might well marvel at the idea that a jury could be expected competently and fairly to assess technical and legal issues as complex as those involved in this case. However, this victory was relatively short-lived (as legal processes go) because it was reversed by the Court of Appeals for the Federal Circuit (CAFC) in June 1994.

While the Appeal to CAFC was pending, Wellcome announced their decision to discontinue development of a t-PA product. Genentech had also decided not to cross-

appeal on the issue of the literal interpretation of the claims. Therefore, the only issue for the CAFC was whether FE1X infringed under the doctrine of equivalents.

The court identified three key issues. The first was whether the specific activity limitation in the '603 patent applied to the '075 and '330 patents, to which the court gave a negative answer because these were in every way independent patents. The second was the basis of measurement of the specific activity figure. The court decided that this was to be measured by the bovine fibrin plate assay. The third and much the most important question for the court was the meaning of 'human tissue plasminogen activator'.

The essential nature and properties of human t-PA had been described in various ways in the patent with the result that the court had to choose from at least the following four possible definitions of the substance:

(i) recombinant t-PA having the structure (composition) of native t-PA.
(ii) products containing the Kringle and Serine Protease regions.
(iii) products containing just the enzymatically active portion i.e the Serine Protease region.
(iv) products which convert plasminogen to plasmin, bind to fibrin, and are classified as t-PA on the basis of immunological properties.

On the evidence of witnesses, the CAFC opted for the first of these definitions because 'it is the most consistent with the limited form in which the claims are drafted, and the others are hopelessly over-broad'. The court concluded that the jury's finding of equivalents was not supported by the evidence on any of the key issues mentioned above. FE1X was also shown to behave significantly differently from human t-PA in the body (e.g. ten-fold increased half-life, decreased binding affinity). Therefore FE1X did not infringe any of the asserted patents.

INFRINGEMENT BY IMPORTATION

Before addressing this topic it will be helpful to review the following basic points about product patents and process patents:

(i) A product patent, for present purposes, is one which claims the product *per se* without limitation as to the process used to make it. This is the claim normally granted where the product is new and can be defined *per se* in physical, chemical, or other structural terms.
(ii) A product-by-process patent is one which claims the product in terms of a particular process of preparation described in the patent. This is frequently used when the product is new but cannot be defined in any of the usually accepted ways.
(iii) A process patent covers the procedural act of preparing a product by the steps defined in the process claim.

It follows that a product patent protects against unauthorized manufacture in, or importation into, the 'patent-country' no matter by what process the product has been made. Before the other types of patent can be exercised, it will be crucial to determine what process has been used either locally or abroad.

One might think that one who imports a product made outside the jurisdiction of the 'patent-country' might be immune from the effect of a process patent. But in Europe, a process patent automatically also covers the product made by that process, with the qualification that it is the direct product of the process. Under the old British law a court generously held that a process patent for making a sulfochloride intermediate in the manufacture of saccharin was infringed by importation of the final saccharin product, even though the latter was some reaction steps away from the particular intermediate.

The first generation of recombinant DNA inventions were directed to the manufacture of known proteins. In both US and European patent practice the product in these circumstances could not be claimed, even in product-by-process terms. Under the more generous UK practice the claim to 'recombinant t-PA' (which is a broad product-by-process claim) was allowed by the UK Patent Office and was not criticized, for being such, in the fateful court action.

The usual types of claim allowed in these circumstances, especially in the US, were those directed to DNA sequences, recombinant vectors, and transformed cells. These products can be fairly described as the 'tool kit' or as 'intermediates' for producing what would be the ultimate commercial product. But if no claims are to be allowed to the recombinant protein, as such, how can the patent owner prevent importation of the latter, even when the same intermediates and processes have been used in the country of manufacture? This difficulty was experienced in the US t-PA litigation, as mentioned above, and also in the erythropoietin litigation described in Review 2.

This loophole in the US law of patent infringement could be a problem also for chemical and other types of invention but the defect was spotlighted as specially acute for biotechnology inventions. From January 1996 an additional ground of infringement introduced into the US patent statute is now available to cover these situations. Importation of a product made abroad by a process which has been patented in the US is henceforth an infringement of the process patent. However, if the product is 'materially changed' by subsequent processes before it enters the US there is no infringement. What constitutes a material change has been considered in a number of pharmaceutical chemical cases and it is evident that this will always be a matter of interpretation by the US courts.

In one biotechnology patent case (Biotechnology General Corp, 1996) the Genentech patent (US 4 342 832) was directed to a method of constructing a replicable cloning vehicle. Biotechnology General, based in Israel, used this method to construct a plasmid which was then used to produce growth hormone. The latter was exported to the US. Here was a case where the product of the patented process (the plasmid) and the exported end-product hGH are totally distinct substances. Therefore, one might have thought that the legal wording could not apply to this situation. However, when this legislative change was pending in Congress, a US Senate Report envisaged precisely this type of case (plasmid and expressed protein) and interpreted the wording more broadly than according to its strict literal sense. Thus, said the Report, if production of the expressed product could not have been commercially viable without use of the actual product of the patented process, there would be infringement. This example illustrates how the legislative history can be important in interpreting the scope of the legal statute.

Patent developments in plant biotechnology

The question of patent protection for transgenic plants and other innovations in plant biotechnology has been bedevilled for many years by the existence of 'plant breeder's rights', the specially created legal system (separate from patents) for the protection of new plant varieties. In European and many other countries (USA and Australia being notable exceptions) the insistence by the official authorities on a clear demarcation between the two legal systems has caused difficulty for the plant biotechnology industry.

In Reviews 2 and 3 it was explained that in many European countries the patent law was originally considered unsuitable for protecting new plant varieties developed by traditional breeding methods. Special national laws of plant breeders' rights (also called plant variety rights) were therefore established in the 1960s in some countries as well as the International Union for the Protection of New Varieties of Plant (UPOV, 1961).

In order to protect the plant variety right system from any interference from the patent system UPOV prohibited the possibility of protection by both forms ('double protection') in Article 2(1), which provided:

> Each member State of the Union may recognise the right of the breeder provided for in this Convention by the grant either of a special title of protection or of a patent. Nevertheless, a member State of the Union whose national law admits of protection under both these forms may provide only one of them for one and the same botanical species or genus.

This restriction was reinforced in the patent laws of those countries that decided to go further and expressly to exclude plant varieties from patent protection, e.g. according to the prototype provision of EPC Article 53(b) which prohibits patents for

> plant or animal varieties or essentially biological processes for the production of plants or animals: this provision does not apply to microbiological processes or the products thereof.

It is noteworthy that the second half of Article 53(b) limits the exclusion. It is believed that this was included to safeguard the patentability of microbial cultivation methods and resulting products e.g. antibiotics.

The term 'essentially biological' has not yet been judicially defined although, as mentioned later, some attempt at clarification has been made in the EPC case law. Bearing in mind the birth of the UPOV legislation, and the desire to ensure that patents would not impinge on plant breeding methods, the term may have been simply intended to apply to the traditional processes used to breed new plant varieties. In spite of the confusion to which this term has given rise, the legislators seem unable or unwilling to dispense with it.

But what is a plant variety? The 'definition' of the plant variety, used in the original 1961 version of the UPOV Convention, in Article 2(2) stated:

> For the purposes of this Convention, the word 'variety' applies to any cultivar, clone, line, stock or hybrid which is capable of cultivation and which satisfies the provisions of sub-paragraphs 1(c) and 1(d) of Article 2.

(the cited sub-paragraphs dealt with homogeneity and stability)

According to this definition, then, a variety was whatever satisfied the criteria of distinctness, uniformity, and stability (DUS) and was therefore protectable under the UPOV Convention. This definition was removed when the Convention was revised in 1978.

As noted in Review 1, in the Ciba-Geigy case, the EPO Technical Board of Appeals held that:

> . . . If plant varieties have been excluded from patent protection because specifically the achievement involved in breeding a new variety is to have its own form of protection, it is perfectly sufficient for the exclusion to be left restricted, in conformity with its wording, to cases in which plants are characterised precisely by the genetically determined peculiarities of their natural phenotype. In this respect there is no conflict between areas reserved for national protection of varieties and the field of application of the EPC. On the other hand, innovations which cannot be give the protection afforded to varieties are still patentable if the general prerequisites are met.

It was therefore the understanding in patent circles that a variety was a sub-group of a plant species (or sub-species) containing individual members which resembled one another phenotypically and complied, for the most part, with a set of listed characteristics which constituted the official description of a protected variety by which it was distinguished from other such sub-groups of the same species. Patent law could live comfortably with such a notion. With the advent of plant biotechnology, patent specialists argued that the above exclusions could not apply to recombinant DNA methods and transgenic plants.

The meaning of 'essentially biological' was considered in the case of Lubrizol Genetics (1990). In the Lubrizol process, parent plants with desired characteristics are selected, test-crossed, marked and stored. The hybrids resulting from the crosses are then evaluated for desired traits and phenotypical uniformity and that pair of parent plants (at least one of which is heterozygous) which provide the desired hybrids is selected. At least the heterozygous parent plant is multiplied by cloning and the crossing of the said pair of parent plants is repeated as often as desired to provide hybrid plants on a large scale.

The Technical Board of Appeal considered that, in a multi-step process, each single step as such may be characterized as biological in a scientific sense. However, in this case the essence of the claimed process lay in the particular combination of specific steps. The totality and the sequence of the specified operation neither occurred in nature nor corresponded to classical breeders' processes. The arrangement of steps in the claimed process represented an essential modification of known biological and classical breeders' processes, and the efficiency and high yield associated with the product showed important technological character.

The Board held that in Article 53 (b) the exclusion of 'essentially biological' processes for the production of plants and animals should be construed narrowly. Whether or not a process is to be considered as 'essentially biological' has to be judged on the basis of the essence of the invention taking into account the totality of human intervention and its impact on the result achieved.

THE EUROPEAN COMMISSION'S PROPOSED DIRECTIVE (1988/1995)

The European Commission's proposal, in October 1988, for a Directive to EC Member States concerning the legal protection of biotechnological inventions accepted the patent case law outlined above as its starting point. In order to ensure that patent protection was available for inventions in plant biotechnology, Article 3 of the Commission's original text of the Directive provided that 'biological classifications other than plant or animal varieties . . . shall be considered patentable subject matter'.

In the course of some years of discussion with official representatives of Member States, this formulation had been modified. After receiving a negative opinion on the Directive by the European Parliament (October 1992) followed by a total Parliamentary rejection of the Directive (March 1995), the European Commission re-vamped many of the controversial Articles and re-submitted a new version of the Directive (1995). The current draft (now Article 4(2)) reads:

> Biological material, including plants and animals, as well as elements of plants and animals obtained by means of a process not essentially biological, except plant and animal varieties as such, shall be patentable.

THE 1991 REVISION OF UPOV (UPOV 1991)

A carefully worded definition of a plant variety now stands at the forefront of this Convention in Article 1 (vi). It states:

> 'variety' means a plant grouping within a single botanical taxon of the lowest known rank, which grouping, irrespective of whether the conditions for the grant of a breeder's right are fully met, can be:
>
> - defined by the expression of the characteristics resulting from a given genotype or combination of genotypes,
> - distinguished from any other plant grouping by the expression of at least one of the said characteristics and
> - considered as a unit with regard to its suitability for being propagated unchanged.

The most significant point about this new definition is that it is no longer to be equated with 'UPOV-protectable variety'.

Another respect in which protection under UPOV has been widened is that, under Article 14 (Scope of the Breeders' Right), the right is to extend to 'essentially derived varieties'. The complex definition of this term given in Article 14(5) will not be discussed here. However, the Vice-Secretary of UPOV has declared (private communication) the view that it would cover a genetically modified variety which retains the whole genome of the original protected variety.

INVENTION, PROTECTION AND EXPLOITATION

The legal principles discussed above may be better appreciated in the light of a concrete practical example. This example is based on European patent publication No 272 144.

The gene responsible for producing a trypsin inhibitor in the cowpea (*Vigna unguiculata*) has been transferred to other genera of plants. The cowpea is a legume,

also called 'black eyed bean', which is grown as a food crop in West Africa and in both North and South America. The trypsin inhibitor produced by resistant varieties of this plant prevents the invading insect from digesting protein so that it dies from starvation. Transfer of the inhibitor gene to other plant genera requires the methods of plant biotechnology and cannot be achieved by traditional breeding methods. The technology is aimed at protecting cotton and cereals against bollworms of the genera *Heliothis* and *Anthonomous* which affect these crops throughout the American and African continents. It is applicable also to protect grain of wheat, maize, rice and sorghum against storage pests of the genera *Tribolium, Sitophilus* and *Chilo*, the latter being particularly serious in Africa, India, China and Japan.

Considering this invention first from the aspect of patenting transgenic cotton plants, the following claims might have been presented:

(i) A transgenic cotton plant having a gene for a trypsin inhibitor.
(ii) A transgenic cotton plant having a gene for a trypsin inhibitor derived from the cowpea.
(iii) A cotton plant of the variety 'Stoneville 825' containing a gene for a trypsin inhibitor derived from the cowpea.

Before the most recently decided EPO case law to be described below, the EPO would allow claims of type 1 and 2 because the plants are not claimed at the varietal level of definition. Each of these claims will cover all manner of varieties of cotton in which the gene has been introduced but patentability is not affected by this fact. The claims are allowable or not depending on whether or not they express an invention, and the plants covered by the claims are not in any sense being patented as varieties but as articles embodying an inventive step.

Claim 3 above is the only claim which mentions a variety and is thereby arguably open to objection. It is a strange result that the patent applicant is apparently barred from specifically claiming the application of his invention to a particular commercially important variety. Since the major crop plants are marketed as varieties, what use would a transgenic plant patent be, if it did not cover such an application. This anomalous result is one unforeseen consequence of the desire to draw an absolute line between the two forms of legal protection. The transgenetic process, whereby the foreign gene enters the genome of the starting variety, will not necessarily result in another variety in the older sense of the term i.e. DUS variety. The process will produce the parental material from which further varieties will be bred. However, as a result of the new variety definition in UPOV 1991, the EPO have changed their attitude to patent claims of the above type.

Before discussing the recent EPO case in which this change has come about, and as a digression from law to practical realities, it will be of interest to discuss the method by which commercial application of the above type of invention would be undertaken.

COMMERCIAL EXPLOITATION

A typical pattern of the creation and exploitation of this type of technology could be as follows. A biotechnology research group in a scientific research institution or in an industrial research laboratory will have isolated the gene from the germ plasm of the

source country and will have patented the gene-construct and the method of gene transfer to the plants targeted for protection. The patent owner will be free to develop and exploit this technology commercially on his own behalf. But it may be better to license the technology to commercial plant breeders in industrially developed countries and to appropriate organisations in developing countries, e.g. State-run agricultural research Institutes, together with the know-how to transfer the gene to chosen types of plant. The plant breeders or research Institutes may obtain plant breeders rights for any resulting varieties. The new varieties will be sold to farmers who will cultivate them and, as a result of their improved pest resistance, will be able to economize in the use of chemical pesticides. The public will benefit from the advantages to the environment resulting from this technology. It is difficult to see who will not gain from this achievement. Unless the transgenic plant enables the farmer to achieve a better yield or a saving on the use of insecticides it will not be worth the higher price asked for it and it will not be purchased.

THE INTERPRETATION OF EPC ARTICLE 53(B)

A recent decision of the EPO Technical Appeal Board (Plant Genetic Systems, 1995) has upturned the hitherto prevailing interpretation of EPC Article 53(b).

Plant Genetic Systems European patent 242 236 was directed to transgenic plants containing in their cells a gene which conferred resistance to the herbicide 'Basta'.

The most important claim (claim 21) was to:

> Plant, non-biologically transformed, which possesses, stably integrated into the genome of its cells, a foreign DNA nucleotide sequence encoding a protein having non-variety-specific enzymatic activity capable of neutralizing or inactivating a glutamine synthetase inhibitor under the control of a promoter recognised by the polymerase of said cells.

The patent also had claims to the methodology for transforming the plant, vectors, plant cells, and seed. It is important to note that the claims were not limited to particular plant species but referred to 'plants' in general. Until this patent was challenged the EPO had been willing to allow patents for plants defined in this generalized way i.e. in non-variety specific terms.

The patent was opposed by Greenpeace, who based their arguments on EPC Article 53 (a) which denies patents on 'inventions the publication or exploitation of which would be contrary to "ordre public" or morality,. . . and Article 53(b) (discussed above)'.

The main attack on the patent was based on the argument that it was immoral to 'own' plants, which were the common heritage of mankind. Greenpeace supported this by producing results of surveys/opinion polls taken in Sweden (only farmers were consulted) and Switzerland.

The Technical Appeal Board considered the morality objection in depth and rejected it. The Board set out principles which they considered relevant to the assessment of such objections and their decision will be of greater use in cases where this objection is more appropriate than in one relating to plant biotechnology inventions. The Board considered the survey data as unrepresentative of attitudes in Member States. Indeed, the Board evidently considered the morality objection mis-

conceived in a case of this kind. As regards 'ordre public' the Board would have considered this if there had been any evidence that exploitation of the patent would 'seriously prejudice the environment'. No such evidence was produced by Greenpeace.

But Greenpeace had also taken the Article 53(b) objection, arguing that the claims to plants and seeds would cover varieties formed from them; also that essentially biological processes were involved. It was argued that the claims 'although cleverly drafted in general terms, were in reality meant to cover plant varieties' which would be contrary to Article 53(b). Furthermore, 'when a claim covered something which was unpatentable, the whole claim was bad'.

Greenpeace must have been surprised to find that whilst they had lost on 53(a), they were to win on 53(b). The Appeal Board was clearly influenced by the fact that in the specific patent Examples of producing the transgenic plant, the process began with named varieties. The Board noted that claim 21 was not drafted in terms of a variety 'because there is no reference to a single botanical taxon of the lowest-known rank' but it held that the claim to transgenic plants 'includes within its scope known plant varieties which have been genetically modified so as to be herbicide resistant . . .' and was therefore not allowable under Article 53(b).

The Board also pointed to the new definition of a variety as given in the revised UPOV 1991 and held that the genetically modified plants were themselves new varieties according to the new definition. The Board held furthermore that the claim could not be allowed under the exception provided by the second half of Article 53(b) (the microbiological process exception) since the process of producing and propagating the transgenic plants, although it involved a microbiological step, was not a microbiological process when considered as a whole.

The Board allowed the claims to the transformation process and claims to plant cells but also rejected claims to plant cells when 'contained in a plant'.

PGS appealed to the Enlarged Board of Appeal, which can review decisions of the Technical Boards in certain circumstances, including those where Technical Board decisions are inconsistent with one another. The Enlarged Board did not endorse the first part of the Technical Board's analysis (that the claim 'included' varieties). On their second point (that the transgenic plants were varieties) the Enlarged Board expressed no opinion, holding that it could not intervene because this was a new point which involved no inconsistency with previous decisions.

The decision of the Technical Board therefore stands as authority which the EPO Examining Division now feel obliged to follow.

Although the process technology can still be patented, the specific refusal of product claims to transgenic plants is a setback for European jurisprudence and for the plant biotechnology industry. This decision will undoubtedly be contested when a suitable test-case arises which can be taken to the Enlarged Board of Appeal.

Biotechnology patents and morality

Patent law is not silent on the question of morality. Morality was been brought into the patent law at least from the time of the Strasbourg Convention (1963) in terms that were later enshrined in European law through the European Patent Convention (EPC, 1973). The EPC has now largely eclipsed the existing parallel national patent systems

in Europe and is the one most used by those who invest heavily in science and technology, especially biotechnology. Article 53(a) of the EPC excludes from patentability any invention 'the publication or exploitation of which is contrary to morality or ordre public'. The corresponding national patent laws contain essentially the same provision.

EPC Article 53(a) has provided a convenient international forum in which the Greens, animal rights campaigners and others have not been slow to promote their particular philosophies. The Opposition to the Harvard oncomouse European patent is the most well-known instance of this, there being no fewer than 17 Opponents, among which the British Union for the Abolition of Vivisection, and Compassion in World Farming, are the two most prominent.

THE MORALITY OF PATENTING

It is necessary first to avoid a common confusion. EPC Article 53(a) is concerned with the morality of certain specified actions. Leaving aside the publication aspect, it is the act of actual exploitation of the particular invention to which the moral test must be applied. Whatever the ultimate intentions of the patent holder, the morality of the act of patenting does not come into the question. The belief that it is wrong to patent certain substances, organisms or processes calls for an ethical judgement that is outside the patent law itself and therefore one that patent officials or judges cannot be called upon to make.

Patenting an invention does not commit the patent holder to any particular course of action. Having a patent may be an encouragement to exploit an invention but exploitation can take place even without a patent, assuming other laws and regulations permit. Patenting, as such, is in itself neither wrong nor right, but could be classed as 'ethically neutral'. To refuse a patent would be a futile gesture that would not by itself stop the invention being put to practical use. However, if Society were to judge that the practice of a particular invention deserved to be banned by law then nobody would bother to patent it.

The various ways in which objections to biotechnology patents are being formulated are summarized below.

OBJECTIONS TO PATENTING 'LIFE'

Microorganisms

Those who object to the patenting of living matter will not allow any exception to their rule. The objection to patenting microorganisms is usually merged into the general charge that patenting 'life' implies a failure to respect life. But society cannot have bread, wine, antibiotics, and vaccines without the industrial use of microorganisms. These products are beneficial and to produce them more effectively by means of improved and patentable strains of microorganism is also meritorious. Patenting the organisms harms nobody.

Plants

Nor does the morality argument sit comfortably when applied to the patenting of plants. Usually the morality objection slides into one of challenging the use of genetically manipulated plants on grounds of public safety. Important though the question of safety undoubtedly is, it is primarily a matter of complying with other laws and regulatory procedures that have been established as matters of public policy. It would doubtless be immoral to act irresponsibly in matters affecting public health but the legal control on this has nothing to do with patents.

Animals

The morality argument appears more pertinent when it comes to the patenting of animals. Here we are dealing with a sentient being and we have to ask whether that makes a difference to the moral issue. It is necessary first to address the metaphysical objection that an animal should never be reduced to the status of an 'invention' let alone a patentable one.

The term 'invention' in patent law has to serve for a wide variety of items that are presented as new and improved over what is already known and used, i.e. over the 'prior art'. Some inventions are startlingly new in their own field but most are improvements or modifications of existing processes and products. These latter kinds of invention may be less original than the 'pioneering' inventions but all that concerns the patent law is whether their difference from the prior art required inventiveness to accomplish or was 'obvious' to the skilled person.

In the case of a transgenic animal it is this difference from the prior art upon which the legal examination focuses. Since this difference does not occur naturally, it is reasonable to describe it as a work of human ingenuity, as man's handiwork rather than that of Nature. The US Supreme Court made this point in 1980 in approving the grant of the first patent on a genetically manipulated strain of bacterium (the Chakrabarty pseudomonas) and it is equally applicable to the higher life forms. The inventor certainly does not undervalue the work of God or Nature which provided the starting point, nor does the inventor claim to have 'created' the whole animal. Of course, the patent has to cover the modified animal as a whole since the difference cannot be used in isolation.

Animal transgenics involves the genetic modification of two main types of animal, laboratory test animals and farm animals. Each of these requires its own special treatment from the moral point of view.

LABORATORY ANIMALS

The Harvard oncomouse is genetically programmed to be more sensitive to carcinogens. In this respect the oncomouse is superior to previously used types of laboratory mouse, which may mean that scientists can use fewer mice than before. It is nevertheless an emotive case, which reinforces the dilemma over the general question of sacrificing animals in the quest for cures for human diseases.

The moral argument against animal experimentation is that the animals are used as mere tools for human ends and in ways that involve suffering. The animal's pain and

in some experiments the indignity for the animal are distressing to many people. But, if this is a real moral issue for humans and not just one of sentimentality, it has nothing to do with the question of patents for improved test animals. It is the fundamental issue that society must settle rather than the side issue of patenting.

FARM ANIMALS

In Britain, ethical issues involved in various aspects of this technology have been addressed by two public Committees.

REPORT OF THE POLKINGHORNE COMMITTEE (1993)

The first of these, the Polkinghorne Committee, was asked to consider 'the moral and ethical concerns (other than those related to food safety) that may arise from the use of food products derived from production programmes involving such (transgenic) organisms'. The Committee did not address wider ethical matters but did discuss the idea of 'moral taint' attaching to foods produced with the aid of genetic modification and deriving from the 'unnaturalness' and any animal suffering that might be involved.

In considering the element of unnaturalness the Committee identified, as the key factor, 'the status of the human genetic material inserted into the farm animal'. The committee distinguished between human genes as existing in the human body and 'copy genes of human origin' The procedure for cloning the gene results in an enormous dilution effect (10^{55}) so that the inserted material is overwhelmingly in the form of synthetic copies of the original. If mRNA cloning is used literally nothing remains of the original gene or message. Accordingly the essential phenotype of the recipient species is not altered. Basing itself on these essentially scientific facts the Polkinghorne committee rejected the idea of 'a moral taint that would warrant a total prohibition on genetically modified food use'.

REPORT OF THE BANNER COMMITTEE (1994)

The second committee, the Banner Committee, considered the ethics of novel farm animal breeding techniques. The committee asked whether there are 'intrinsic' objections to certain types of genetic modification that cannot be overcome by 'consequentialist' arguments. According to the consequentialist view of ethics the morality of an action is to be judged (only) by its consequences. This usually entails balancing the benefit against the harm resulting from the action. An intrinsic objection is one not related solely to the consequences of a particular practice or action but to the practice or action itself.

In genetic modification the Banner committee considered that there is a line between what is acceptable and what is not. Whilst this cannot be drawn sharply, the committee felt that 'harms of a certain degree or kind ought under no circumstances to be inflicted on an animal'. One prominent theme in this connection is that of naturalness, contrasted with modifications which threaten the achievement of the animal's 'natural ends or good' or do not respect its 'essential nature and well-being' or its 'natural characteristics and form'.

For example, the use of gene technology to increase the protein content of cow's milk or to cause poultry breeding stock to produce only female chicks could be achieved whilst still respecting the essential nature and well-being of the animal. These were therefore not considered intrinsically objectionable modifications. However, to increase the efficiency of food conversion in pigs by reducing the sentience and activity of the animal was to disregard the ends and purposes which are natural to pigs and was intrinsically unacceptable.

Asking whether there might be reasons for prohibiting patents in this field the Banner committee rejected most of the anti-patent arguments. However, having concluded that some instances of genetic modification are acceptable and some not so, it felt that the patent law should discriminate between these. Having passed this heavy burden to the patent authorities, the Banner committee went on to dismiss the provision in the proposed EU Directive on this subject (see later) which would have denied patents for 'processes for modifying the genetic identity of animals which are likely to cause them suffering or physical handicaps without any substantial benefit to man or animals, and animals resulting from such processes'. The committee were not convinced that this was a workable and appropriate provision since it left so much open to question.

This Directive was voted down by the European Parliament in March 1995 but a revised version was re-presented by the Commission in December 1995. In the new draft the above provision has been retained, but with the added wording:

> insofar as the suffering or physical handicaps inflicted on the animals concerned are out of proportion to the objective pursued.

Patenting material derived from human tissue

Patents have been granted on materials isolated from human tissues and some have been challenged, including the following two examples:

THE JOHN MOORE CASE

John Moore has expressed concern over the fact that cells taken from his spleen have been immortalized and patented by his physician and the University of California. John Moore's cancerous spleen had been removed by his physician who then, apparently without his patient's consent, researched its cell content and developed a useful and patentable cell line. The patent (US 4 438 032) covers a single cell suspension of the Mo cell line and various proteins produced from it.

John Moore sued both the physician and the University. On the intellectual property ownership issue Moore's claim was not upheld by the California Supreme Court. The court decided that he was not entitled to claim ownership of the intellectual property in the cell line. The patented cell line, though developed from the spleen cells, was held to be different from the cells actually removed from the patient. Moreover, the court was of the view that to grant to the 'donor' of an organ the intellectual property in anything developed from it would inhibit research of this kind. John Moore nevertheless continues to believe that others have patented and now 'own his genetic essence'.

THE RELAXIN CASE (1995)

The Green Party opposed European patent 112 149 granted to the Howard Florey Institute of Experimental Physiology and Medicine for a gene sequence coding for human relaxin, a hormone involved in reproduction. The gene was isolated from ovarian tissue removed in the treatment of an ectopic pregnancy.

One of the Opposers' arguments was that it is 'an offence against morals to exploit the pregnancy condition of a woman by removing tissue from her ovary and using it as the basis of a profit-oriented technical process'. The Opposers also raised the bizarre (in my opinion) objection that the use of the ovarian tissue for the purposes of the patent 'involves dismemberment of women and their piecemeal sale to commercial enterprises'.

The Opposition Division roundly rejected these objections. The tissue had been provided with patient consent; it was perfectly acceptable to use such material; DNA is not 'life'; a human being cannot be reconstructed from the sum total of human genes; and many other reasons were given for dismissing the arguments as thoroughly misplaced.

ETHICAL VIEWS OF VARIOUS ORGANIZATIONS

Ethics in science and medicine

The consequentialist view of morality seems to be the 'establishment' view of science and medicine. The use of experimental animals is justified in the following exemplary quotation by Lord Adrian, President of the Research Defence Society: (Adrian, 1991)

> The use of living animals in scientific research can be considered justified if it is likely to produce appreciable benefit to society, if there is no other way to conduct the research in question and if all reasonable steps are taken to keep any distress or suffering to a minimum.

A very large percentage of the public would probably agree with this position. It also appeals to lawyers. In the European patent application for the Harvard Oncomouse the Technical Appeal Board instructed the Examining Division of the European Patent Office (EPO) to consider the morality issue under Article 53(a). The Board suggested that the decision 'would seem to depend mainly on a careful weighing up of the suffering of animals and possible risks to the environment on the one hand and the invention's usefulness to mankind on the other'. The Examining Division decided that the likely benefit to cancer research outweighed the other factors and granted the patent.

This 'balancing principle' is criticized by the Opponents of this patent who say that an intrinsically immoral act cannot be justified by the fact that some good consequences ensue. This argument rests on the unproven first premise that it is immoral to alter the genes of animals and especially so if it results in animal suffering.

Official and patent professional views

The professional Institute of European patent attorneys (EPI 1993) has stated its view on the subject from a practical standpoint. The EPI support the official view of Article

53(a) as expressed in the EPO Guidelines, where it is stated that:

> This provision is likely to be invoked only in rare and extreme cases. A fair test to apply is to consider whether it is probable that the public in general would regard the invention as so abhorrent that the grant of patent rights would be inconceivable.

EPI also endorse the view of the EPO Opposition Division that:

> Only in those very limited cases in which there is an overwhelming consensus that the exploitation of an invention would be immoral may an invention be excluded from patentability under Article 53(a).

As to the test suggested by the Appeal Board, which is evidently to be used as a standard for transgenic animal cases, the EPI observes that it will often be very difficult if not impossible for patent officials to assess the benefit against the harm of particular inventions, since these may be fully revealed only in the longer term and not at the early stage at which patent applications are examined.

The EPI much prefers the 'overwhelming consensus' test as the ultimate criterion for the purposes of Article 53(a) and sees the balancing principle as just one factor contributing to the assessment.

The Nuffield Council

The Nuffield Council has addressed patent issues in Chapter 11 of its recent report (Nuffield Council on Bioethics). This is a lucid summary of the issues involved in patenting inventions derived from human tissue and it discusses the following options for resolving problems.

One option is to remove the morality issue from the remit of the Patent Office and to leave it to national courts. The Council notes the disadvantages of this option, especially the likelihood of different national treatment and the resulting confusion.

Another option is the 'light approach', favoured by two former Comptrollers of the UK Patent Office. This is a variant of the first option in which the Patent Office invoke the objection only in extreme cases, leaving it to national courts to sort out remaining problems. This corresponds to the present attitude of the EPO in examining patent applications. How it would work in the face of a determined third-party Opposition to the patent is far from clear.

A third option is to transfer the responsibility from the patent examiners to a specially constituted ethics committee, which would become part of the official process either before or after grant of the patent.

The fourth option, which is most favoured by the Nuffield Council, is for the creation of a protocol to the EPC setting criteria for national courts in applying the immorality exclusion. Bearing in mind the predominant role of the EPC in the European patent scene, any scheme that retains the immorality exclusion in the law of the EPC but aims somehow to exclude or mitigate its rigorous application during the European phase of the patenting process may not be viable.

OTHER OBJECTIONS: PATENTING GENES

Those who object to biotechnology patents do not restrict themselves to raising moral objections. They are also ready to deploy patent law arguments as part of their strategy. This can be seen in their criticism of gene patents.

DISCOVERY OR INVENTION?

The law says that inventions are patentable but discoveries are not. The objectors argue that because genes exist in Nature they cannot be invented but only discovered. The distinction between discovery and invention is difficult to define in any of the sciences of Nature because the act of discovery so closely underpins the resultant practical application which constitutes the invention. As ethicist W.Ch. Zimmerli has put it (Zimmerli, 1994):

> every scientific discovery, if made technologically applicable, becomes an invention.

The official patent authorities are not prepared to dismiss the isolation of genes as mere discovery. There are many judicial statements to this effect but the objection persists.

THE QUESTION OF NOVELTY

Another argument against patenting genes is that, because of its pre-existence, a gene cannot fulfil the patent law test for novelty. But this test is framed in terms of availability to the public. Thus it focuses only upon what is already in the public domain through public disclosure or use before the filing of the patent application.

Genes do not easily fit into this scheme. To be made available to the public the gene must first be isolated, preferably sequenced, and cloned. The contribution to the art on which gene patents are based is the making of the gene available in a form that can be utilised to produce an expression product, and to produce this in quantity, for example, as a commercial pharmaceutical product. Alternatively, the cloned gene can be used to transform an organism of another species giving rise to new products, e.g. transgenic plants and animals. Genes are therefore a special case of the broad class of naturally occurring substances that in appropriate circumstances can be patented. Mere pre-existence of the substance, in association with vast quantities of other materials, is insufficient to overcome the objection. This is the official legal view.

THE QUESTION OF INVENTIVE STEP

Those who describe DNA sequences as 'mere discovery' are now latching on to the argument that however difficult gene cloning was in the early 1980s it is becoming routine in the laboratories of today. Whatever may be the state of current general skill and knowledge in relation to these techniques this argument is only relevant to the question of inventive step, i.e. as to how much ingenuity is required to isolate genes. This evaluation must always be made case by case and no broad general dismissal is justified.

In answering this question, patent officials have recognized the distinction between the genes of lower organisms and those of higher life forms. They have noted that, whereas prokaryotic genes are transcribed in full, the messenger in eukaryotic gene transcription is an edited form of the primary RNA transcript. Consequently the DNA made by enzymatically copying mRNA into cDNA is not the natural gene as such.

In summary, objections of the type considered here have so far been singularly unsuccessful when applied against European patents. Nevertheless these interventions add to the expense of patenting and cause uncertainty to the innovators.

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