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Microbiological Inventions and the Patent Law—International Developments

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Introduction

The first review of this subject to appear in this series (Crespi, 1985) was intended to serve as an introduction to basic notions of patent law as they affect inventions in biotechnology. Without such an introductory treatment it would be difficult to appreciate the issues underlying many of the current disputes involving industry and other users of the patent system and those government officials who are custodians of the patent law and guardians of the public interest. As the earlier review showed, applicants for patents have to contend with official examining authorities over the interpretation of a number of legal questions which have become more complex as the science and technology of biotechnology have themselves developed. In addition to the controversy at this level, industrial competitors are locked in a number of court battles over rights to some of the more important developments in biotechnology that are showing significant commercial potential. In the earlier paper the basic conditions for patentability were outlined, as well as the types of patent that can be obtained in this field. These topics were described in the context of a historical development leading to the type of patent law that exists today and the problems the law poses for workers in industry and research institutions and for those who have the responsibility for exploiting the inventions that arise in these varied environments. The situation outlined in the previous study

Abbreviations: AIPPI, Association for the Protection of Industrial Property; ATCC, American Type Culture Collection; cDNA, complementary DNA; CPC, Community Patent Convention; DNA, deoxyribonucleic acid; DUS, distinctiveness, uniformity and stability (of varieties); EC, European Commission; EEC, European Economic Community; EPC, European Patent Convention; EPO, European Patent Office; ICDA, International Coalition for Development Action; IFNα, α-interferon; mRNA, messenger RNA; OECD, Organisation for Economic Cooperation and Development; OTA, Office of Technology Assessment; t-PA, tissue plasminogen activator; UPOV, International Convention for the Protection of New Varieties of Plants; USPTO, US Patent and Trademark Office; WIPO, World Intellectual Property Organization.

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(Crespi, 1985) was especially complex in its international aspects because of differences between national regulations and in the interpretation of them by the various authorities concerned. One major work to be published since the 1985 review began with the following depressing statement:

> Yet where one specific kind of innovation – biotechnology – is concerned, the relative worldwide harmony in intellectual property law gives way to discord of a magnitude discouraging even to the most optimistic proponents of international uniformity. Admittedly, there is widespread agreement now that 'biotechnology' involves uses of, or organic changes in, animals, plants, microorganisms and any biological material that can be assimilated by living matter. But beyond this broad definitional consensus, there lie profound differences dividing the nations over how, or even whether, the diverse fruits of biotechnology should be protected. (Bent *et al.*, 1987)

It may be difficult at first sight to appreciate why inventions in biotechnology cause such problems in patent law. However, the living nature of the material with which the biotechnology inventor works has certain consequences of a special kind. The first consequence is that the material is usually too complex to be described in the degree of precision which the patent law demands for the writing of patent specifications. Secondly, the material is capable, given some help from the human operator, of multiplication to supply vast quantities of itself from the smallest amounts of starting material. These two important differences from other inventions are the primary reason for the problems outlined in the earlier review. It may also be difficult to see why these problems have not yet been solved, given that all the necessary structures and organizations, both public and official and private and industrial, which could bring about such a desirable state of affairs, are already well established and indeed highly active. It is the purpose of this review to examine recent developments, and to describe the present state of this wide-ranging debate. To begin, it is necessary to recall how international co-operation is managed in this field of law.

International co-operation

OFFICIAL CIRCLES

The prime instrument of international co-operation in the intellectual property field on a world scale is the World Intellectual Property Organization (WIPO) based in Geneva. There is also an on-going collaboration between the Patent Offices of the United States, Japan and Europe which is styled 'Trilateral Co-operation'. On a more restricted scale, there is co-operation between the contracting states of the European Patent Convention (EPC) and of the European Economic Community (EEC). In Europe the most important recent

development is the European Commission's (EC) proposal for a directive on this subject to EC member states (European Commission, 1988).

WIPO works through the system of Committees of Experts, these being spokesmen primarily for the national Industrial Property Offices. The Committee of Experts on Harmonization should be noted first because it aims at the conclusion of an International Treaty. However, it has barely begun to consider the problems of particular technologies and it is doubtful whether it could come to grips with special biotechnology issues in the short term. The harmonization study will, however, deal with the question of novelty in patent law in relation to publications made by inventors before they have sought patent protection; at present any such publications will prevent any possibility of subsequent patent protection. This question affects inventors in every branch of technology but is one of special sensitivity in the field of biological research. Because of its general nature, discussion of this topic will be reserved for the final section of this review.

Secondly, there is a Committee of Experts on Biotechnological Inventions which has had four meetings in as many years. No treaty will emerge from this project but a series of 'Suggested Solutions' of the special problems of patent law relating to biotechnology will be formulated. At its recent session in Geneva this committee discussed WIPO documents covering the whole range of inventions in biotechnology (WIPO, 1988). The Committees of Experts represent governments. Industry and the professions, known collectively as 'interested circles', send observers to these meetings. Observers can express their views but the acceptance of such views depends on their adoption by one or more official representatives or by the WIPO Secretariat. Many of the suggested solutions have been based on the views of interested circles, but these meetings seem to be more a forum for discussion than an occasion for taking positive decisions.

THE INTERESTED CIRCLES

The largest of the various groups of interested circles is the world-wide patent fraternity known as the Association for the Protection of Industrial Property (AIPPI). The April 1988 resolution of AIPPI on this subject is as follows:

> All prohibitions on the patentability of living things, be they plants, animals or other organisms, or of processes for obtaining them which exist in national laws and international treaties, especially the European Patent Convention, should be abolished as soon as possible.
>
> Since such a change will take time to achieve, during the interim period the present provisions should be interpreted so as to provide the minimum limitation on patent protection. AIPPI endorses the proposals of WIPO in suggested Solutions 1 and 9 of Document BIOT/III/2, dated 8th April 1987, which are to the effect that patent protection should be allowed for all plants or animals when produced by patentable processes and for plants, plant materials or animals other than plant or animal varieties as such; it being understood that the effects of such patents are

not affected by any existing exclusion of plant or animal varieties from patent protection. (AIPPI, 1988)

The same fundamental standpoint is taken by almost all the other groups representing industry and the professions, which are too numerous to mention individually.

CURRENT DEVELOPMENTS

The main developments in what might be termed classical biotechnology are those concerning the way in which micro-organisms, cell lines and other lower life forms are defined and described for patent purposes; on this aspect European law has been relatively static whereas US court-made law has taken a further turn, requiring the issue of new rules for the deposit of such organisms in culture collections. The controversies on this subject described in the earlier review (Crespi, 1985) are by no means resolved yet. The debate still centres on the stage in patent procedure at which the deposited culture must be made available to other persons, including the applicant's competitors. The compromise solution whereby access to the deposited strain can be restricted to independent experts in the period between first publication of a patent application and the eventual grant of the patent is now more widely accepted, having spread from its first appearance in the European Patent Office to its subsequent acceptance in National Patent Offices. The issue which has moved into greater prominence, however, is the question of patents on the higher life forms, especially plants and animals, and important developments have taken place in this area in both European and United States practice. In the area of litigation more can now be said regarding the attitude of patent offices and courts to patents in the recombinant DNA and hybridoma technologies and, in view of the lively current interest in these more immediate practical problems, the following discussion will begin with these issues. The other topics, which are more concerned with legal policy, can best be discussed in connection with the European Commission's Directive in which they occupy a central position.

DEVELOPMENTS IN CASE LAW

The t-PA case

There has been world-wide interest in the struggle between Genentech and the Wellcome Foundation over Genentech's UK patent for tissue plasminogen activator (t-PA), and it is therefore a good example with which to begin. t-PA converts plasminogen into plasmin, the enzyme that breaks down fibrin clots formed in coronary thrombosis, and it therefore has a large potential market. Britain has been the arena for the first patent litigation on this major biotechnology product, but the judgement of the UK courts will undoubtedly have repercussions internationally.

In the British t-PA patent (2,119,804) Genentech obtained claims for the recombinant protein product as such, and correspondingly broad process

claims, and did not restrict themselves to any detailed process of making t-PA limited to the use of the particular plasmids chosen to carry the t-PA cDNA into the particular host cells used by Genentech to express the protein product. This case was therefore a prototype for other patents in the pipeline, filed by Genentech or by other applicants, covering other blood proteins including Factor VIII, antithrombin and serum albumin as well as a number of other proteins of medical importance. The success or failure of the t-PA patent might well be a pointer to the future evaluation of the patent system in relation to biotechnological products of this kind. It was not surprising, therefore, in view of the unfavourable decisions for the patentee that some commentors began to suggest that another type of legal protection should be devised which would recognize with more certainty the achievements of those who are first to succeed in producing valuable proteins by this powerful technique.

To appreciate the issues in the t-PA case it is necessary to recall how patents are constructed. The two-part structure of the patent specification consists first of the technical description that sets out the nature of the invention and instructs the skilled worker how to reproduce it for himself. The second part consists of the legal definitions, known as the 'claims', which circumscribe the scope of the protection that the patent gives. The claims are verbal formulae defining the protected technology in terms of process, product, use or some other category. For a recombinant DNA patent it will be usual to have claims of the following type:

1. Recombinant protein products (and alleles, variants, derivatives);
2. DNA sequences coding for the products, as in (1);
3. Vectors containing the DNA sequences of (2);
4. Micro-organisms, cell lines and other organisms transformed with vectors (3);
5. Processes of producing products as in (1) by expression of DNA sequences (2) in a recombinant host organism.

As regards the interpretation of patent claims, the literal wording is important although the courts have always allowed some elasticity in interpretation in order to catch a clever evader of the strict literal wording. The European Patent Convention aims at striking a balance between the extremes of the tight literal wording on the one hand and the woolly statement of uncertain scope on the other. British law must follow European law in this respect.

As explained in the previous review, a claim to the product itself (*per se* claim) is possible when the product is new, not described in the prior art, i.e. in any published form. But where the product is not new *per se*, but only the process for making it is new, it is often possible to claim the product as made by the particular process (product-by-process claim). As human t-PA was not a new substance at the priority date of Genentech's first patent application (in the USA), it was appropriate to use the more restricted product claim as exemplified by claim 3 in the t-PA patent which reads:

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

Patent disputes centre almost entirely upon the claims. The patentability conditions of novelty, inventiveness and industrial application or utility must be met before any valid patent can be granted. The other main condition is the necessity for a sufficient or 'enabling' disclosure. The disclosure requirement is applied to the technical description given by the inventor, but if directions given to make the claimed product or perform the claimed process are seriously defective then the patent will be invalid.

To dispose of a common misunderstanding, it is incorrect to assume that products of nature cannot be patented on the ground that, by reason of their prior existence in nature, they cannot be novel. Patent law has become much more liberal on this point in recent times by taking into account the merit of first discovery, isolation and the provision of a product in a useful form for therapeutic or other purposes. The European Patent Office guidelines follow this approach and endorse the patentability of natural products in the proper circumstances. Of course, t-PA had been isolated from human tissue before Genentech began work and the identical product had also been produced by culture of the Bowes melanoma cell line. The t-PA claim quoted above was therefore appropriate. As defined, the product is a product not of nature but of a non-natural process.

Genentech based its case on the position stated in the patent itself:

> The present invention arises in part from the discovery of the DNA sequence and deduced amino acid sequence of human plasminogen activator. This discovery enabled the production of human plasminogen activator via the application of recombinant DNA technology, in turn, enabling the production of sufficient quality and quantity of material to initiate and conduct animal and clinical testing as pre-requisites to market approval, unimpeded by the restrictions necessarily inherent in the isolation methods hitherto employed involving production and extraction from existing cell culture. This invention is directed to these associated embodiments in all respects.

The Patents Court held that broad product claims such as claim 3 would only have been acceptable if the patentee had been the first to discover t-PA or its desirable properties. Although Genentech had been the first to identify the DNA coding sequence and to deduce the amino acid sequence of the protein ('a remarkable job of work' which 'involved laborious and costly effort') it had already been recognized by other workers as desirable to produce t-PA in quantity by recombinant DNA methods. These product claims were therefore too wide in being directed to an obviously desirable and potentially possible end reached by routes on which only limited guidance had been given. Only a limited process claim could be upheld in these circumstances.

In the Appeal Court at least four crucial questions emerged: What precisely did Genentech *invent* as opposed to merely *discover*? What scope of claim

would properly reflect what they invented? Was the claim to recombinant t-PA obvious to the skilled worker at the relevant date? What level of skill and knowledge would the hypothetical ordinary skilled worker be assumed to have in relation to the previous question?

Genentech stuck to their ground that the discovery of the sequence was the key contribution, the 'one log holding up the log jam' in the way of progress to the desired product. But both British and European law state that a discovery, as such, is not patentable and it is universal law that you cannot patent knowledge itself but only its practical application.

On the scope of claim 3 Genentech pursued a very bold line in arguing that the discovery of the cDNA sequence led not only to the production of the recombinant form of natural t-PA having the amino-acid sequence 1–527 shown in figure 5 of the patent drawings, but opened the way to modifications of the natural molecule, e.g. by site-directed mutagenesis of the underlying DNA, while preserving the essential t-PA-type activity. This extension of the claim was not significant as regards Wellcome's intended product but shows that Genentech were seeking to dominate a wide range of second and subsequent generation products in this field. To claim for the t-PA patent the status of a master patent on the basis of discovering the sequence of t-PA alone would seem to be remarkably daring. The Appeal Court found this far-reaching proposal unacceptable and were not prepared to sustain claim 3 even if limited to the recombinant equivalent of the natural product. Thus, it was said, the 'contention that Genentech should be protected against any use of this information howsoever this may be achieved in the future is . . . not a claim to a method embracing the discovery but rather a claim for protection of the discovery as such.'

The argument that something is obvious because a number of research groups are working along similar lines has sometimes been used in litigation on patents for new chemical compounds but has not been well received. In this case it succeeded, as seen in the following extracts:

> It is agreed between the experts that at the relevant time, in early May 1982, the production of quantities of t-PA adequate to treat human patients suffering from blood clots was known to be a desirable objective and it is further agreed that the Bowes melanoma cell-line was then available and was known to be a source of t-PA and of the corresponding m-RNA. It was of course then known that the nucleotide and amino-acid sequences of t-PA existed, though their composition was not known. All the steps taken by Genentech in finding out the composition of the sequences and applying that knowledge to produce human t-PA, as defined in the specification, by recombinant DNA technology were applications of known technology, and no step was by itself inventive.
>
> . . . it was indeed obvious, in my judgement, to the person skilled in the art to set out to produce human t-PA by recombinant DNA technology. At least four teams did just that at about the same time. The evidence of those at Leuven and Umea as to their choice of projects is particularly

> relevant. The end was a known desiderandum, and to proceed by oligonucleotide probing was, if not the first choice of each team, an early choice which lay in the way, ready to hand.

Wellcome thus persuaded a majority of the court that the product claims were invalid because they were not only conceptually obvious but also because their practical realization involved no inventive step. However hard this judgement may seem, it simply results from the application of standard patent law principles to the cloning of DNA encoding naturally occurring proteins, and it has been for some time an open question as to whether this involves invention as distinct from experimental skill and the application of sufficient resources. It is difficult to see how any different legal system would cope better with the situation. Copyright as an alternative to patent law is a blind alley in relation to DNA sequences and no other new system is yet on any lawyer's drawing board. Moreover, the difficulties are not nearly as great for newly isolated natural proteins and the products of protein engineering, where the question of inventiveness will return to the more familiar field of new compound chemistry. It would be premature, therefore, on the basis of a transitional problem to despair of the patent system for the protection of innovation in biotechnology.

Genentech have not appealed to the House of Lords and therefore this decision settles British law for the present on the allowability of product claims of this broad type in similar circumstances and against a similar prior art background. However, Genentech will shortly be granted a European patent on a parallel patent application in the European Patent Office and so the matter is by no means concluded. Most of the European claims are in process form, i.e. relate to processes, and there is a noticeable absence of a claim exactly equivalent to claim 3 of the British patent. However, European law states that a process claim gives protection for the product of the process and therefore broad process claims are of considerable value. There is also a product claim to derivatives of the specific 527 amino-acid sequence of native t-PA 'by way of amino acid deletion, substitution, insertion, inversion, addition or replacement'.

To complete the t-PA story for the time being, it should be noted that Genentech have a corresponding United States patent granted in August 1988 (4,766,075). This claims the DNA sequence encoding t-PA and expression vectors and transformed micro-organisms containing this DNA, but the final t-PA product is not claimed. Litigation on the US patent has also been commenced. Also, shortly before this patent was issued, the Leuven workers obtained a US patent (4,752,603) on human plasminogen activator based on their original work with material derived from human melanoma cells. This claims the product in terms of specific activity figures rather than by any specific method of preparation. A general point is worth making here. Although a patent may be based primarily on a method of isolating or purifying a natural product, it may contain product claims which are so worded as to cover a synthetic form of that substance or, indeed, any other artificially prepared form of that substance, e.g. a recombinant product. A situation of this kind arose in the next case to be discussed.

Factor VIII litigation

The antihaemophilic procoagulant activity protein, factor VIII, is the subject of on-going litigation in the USA. The Scripps Clinic and Research Foundation first obtained a patent (US 4,361,509) for a process for the separation of factor VIII:C from factor VIII:RP and for the product of such a process. The claims of this patent were primarily directed to a method of adsorbing the VIII:C/VIII:RP complex from plasma or a commercial concentrate onto a monoclonal antibody specific to VIII:RP. The VIII:C component is then eluted and adsorbed on another column and further concentrated, purified and recovered. The patent also included a product claim in terms of the highly purified and concentrated VIII:C prepared by this method. Under United States patent practice it is possible, if the patentee considers that his patent is defective in certain respects, to surrender the patent and replace it by a 're-issue' patent in which the defect has been cured. Scripps used this highly convenient procedure to obtain re-issue patent number 32,011 with the addition of broader claims of which the following is the most important:

> A human VIII:C preparation having a potency in the range of 134 to 1172 units per ml and being substantially free of VIII:RP.

This claim is directed to the defined product itself and is not restricted by reference to any particular method of preparation. This patent is therefore an example of a patent for a purified natural substance defined in terms of the property of potency within a given range. The experimental section of the patent is restricted to the recovery of the pure protein from natural sources rather than by the methods of genetic engineering. Scripps brought an action against Genentech for infringement through their manufacture of a plasma-derived factor VIII:C preparation and also of a recombinant factor VIII:C. It is in relation to the latter product that the case is of greater interest from the point of view of interpretation of patent claims. Genentech argued that the term 'human' in the above claim should be interpreted to mean 'derived from human blood plasma' in which case their recombinant VIII:C would have been outside the literal scope of the claim. The court rejected this interpretation and its reasoning is illustrated in the following quotations:

> The prosecution history thus makes clear that both Scripps and the examiner considered the term 'human VIII:C' to be descriptive not of its derivation from human plasma but of its fundamental characteristics peculiar to the species. Such characteristics as amino acid sequence, antigenicity, and efficacy in therapeutic use distinguish the factor VIII:C of different species.
>
> The production of Genentech's recombinant factor VIII:C, although it takes place in hamster rather than human cells, is directed by the controlling human gene. That gene, transplanted from a human cell to a hamster cell, determines the amino acid sequence and other fundamental structural traits and functions of the protein.

Genentech have sought patent protection for recombinant VIII:C but even if this were granted it would not thereby free their product from dependence on the Scripps patent. However, this case is not yet over. The above decision was given in an action for preliminary injunction but the case is now under full trial in which the validity of the Scripps patent has been challenged. In the present phase of the trial it is being questioned whether Scripps acted in a legally impeccable manner in broadening their product claims by the use of the re-issue procedure.

Some of the salient features of the factor VIII case can also be found in the following case to be discussed, which concerns erythropoietin, the naturally occurring protein in the blood which stimulates the production of red blood cells.

Erythropoietin litigation

One of the parties to this dispute has a patent for a purified form of erythropoietin while the other has a patent covering recombinant techniques for producing the protein. The case throws further light on the question of mutual impact between two patents of this kind.

The plaintiff, Amgen Inc., holds US patent 4,703,008 (the '008 patent) which describes the production of recombinant erythropoietin. This patent is a good example of the type of descriptive writing which patent attorneys have developed for patents in this field. The patent is very clear and provides a mini-course in molecular biology for the uninitiated, leading the reader step-by-step through the cloning strategy to arrive at the desired product. In US patents based on the cloning of known naturally occurring proteins a common form of claim structure is one based mainly on DNA sequences. Here the text states that:

> The present invention provides, for the first time, novel purified and isolated polypeptide products having part or all of the primary structural conformation (i.e. continuous sequence of amino acid residues) and one or more of the biological properties (e.g. immunological properties and *in vivo* and *in vitro* biological activity) of naturally occurring erythropoietin, including allelic variants thereof.

However, the patent has no claims to the final products, and no claims to methods of producing the final products. The claims are of the following types:

1. Purified and isolated DNA sequences encoding erythropoietin;
2. DNA vectors for transporting such DNA sequences into host cells; and
3. Host cells transformed or transfected with such DNA sequences.

The following two claims are illustrative:

> 1. A purified and isolated DNA sequence encoding erythropoietin, said DNA sequence selected from the group consisting of:

> (a) the DNA sequences set out in FIGS. 5 and 6 of their complementary strands; and
> (b) DNA sequences which hybridize under stringent conditions to the DNA sequences defined in (a).
>
> 7. A purified and isolated DNA sequence consisting essentially of a DNA sequence encoding a polypeptide having an amino acid sequence sufficiently duplicative of that of erythropoietin to allow possession of the biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells, and to increase hemoglobin synthesis or iron uptake.

The defendants in this case are Chugai Pharmaceutical Co., the licensee of US patent 4,677,195 (the '195 patent) granted to Genetics Institute Inc. for a method of purifying erythropoietin. Although the '195 patent mentions cultures of recombinant cells as one possible source of erythropoietin to which the method can be applied, it does not describe the use of such source material in detail in the patent examples. The latter are restricted to the preparation of homogeneous erythropoietin from a mixture of several polypeptides, of molecular masses ranging from 30 000 to 70 000 daltons, derived from human urine. The process is based on the use of reverse-phase high-performance liquid chromatography and is applicable to crude erythropoietin 'no matter what the source of the EPO [erythropoietin] is . . .'. The patent has the following product claim:

> Homogeneous erythropoietin characterised by a molecular weight of about 34,000 daltons on SDS PAGE, movement as a single peak on reverse phase high performance liquid chromatography and a specific activity of at least 160,000 IU per absorbance unit at 280 nanometers.

Amgen failed to persuade the court that its recombinant erythropoietin did not meet the characteristics specified in this claim. The court observed that it makes no difference to infringement liability that Amgen's erythropoietin is produced by genetic engineering. The '195 patent includes product claims, the court explained, and it makes no difference by what path or process the infringing material is manufactured. If Amgen's material produced by recombinant technology falls within the claims of Chugai's asserted product claims, the court reasoned, then Chugai's asserted patent claims are infringed. Moreover, Amgen's counterclaim that Chugai's recombinant erythropoietin imported from Japan infringes the '008 patent did not succeed in the summary judgement phase of the trial. As the Amgen patent contains no claims to the recombinant erythropoietin product and no process claims for making such a product (the latter having been refused by the US Patent Office) the court had to decide the question of infringement on the basis of the claims to the recombinant DNA starting materials and the corresponding genetically manipulated host cells, all of which would have been used abroad and therefore outside the jurisdiction of the US court. This is a tricky question of law and one

on which more may well be heard, if not in this case then in some other. It is clearly important for US patentees to know whether patents with only claims of this type can prevent importation of final expression products. The importance of process claims in the present context arises from the fact that US patent law was amended in August 1988 to bring into effect a provision whereby such claims can now prevent importation into the US of products made abroad by the same process.

The α-interferon (IFNα) case

The work of Biogen on the production of recombinant interferon is the subject of US patent 4,530,901 and European patent 32134. The first patent application filed by Biogen for this work is dated in January 1980. At that time, the patent states, there was a lack of sequence information for the interferon gene and a serious problem of isolation of the desired DNA in view of its exceedingly low concentration in a complex mixture. The US patent includes claims to the relevant recombinant DNA molecules but these take a different form from what I have previously quoted. There are also claims to unicellular hosts transformed with the DNA and there are method claims for producing a polypeptide by expression in an appropriate host. The European patent contains similar claims and also product-by-process claims to 'an α-type interferon produced by a transformed host' as defined in earlier claims.

The European patent was granted in 1984 but was then opposed by nine companies. It would be impractical to reproduce here all the claims originally granted as well as the many amended versions put forward by Biogen during the opposition proceedings. However, claim 1 of Biogen's main request is summarized below:

> A recombinant DNA molecule for use in cloning a DNA sequence of the interferon-α type, said recombinant DNA molecule comprising a DNA sequence from
> a) the DNA inserts of . . . recombinant DNA molecules carried by . . . [a list of various deposited micro-organisms]
> b) DNA sequences which hybridise to any of the foregoing DNA inserts and which code for a polypeptide of the IFN-α type, and
> c) DNA sequences which are degenerate as a result of the genetic code to the DNA sequences and inserts defined in (a) and (b) and which code for a polypeptide of the IFN-α type.

This claim covers recombinant DNA molecules coding not only for naturally occurring α-interferons but for any polypeptides of 'the IFNα type'. Also, by the language used in (b) and (c), Biogen were covering *all* recombinant DNA molecules which would code for the products and not only the particular sequences they had themselves cloned and deposited in the Deutsche Sammlung culture collection [listed in part (a) of the claim]. This is certainly understandable since if the patent were restricted to the latter sequences, it might be easily circumvented.

In an extremely harsh and formalistic decision the Opposition Division rejected the Biogen patent in its entirety. It held that the presence of the claimed DNA inserts in a publicly available gene bank (Lawns gene bank) and the possibility of screening for them by direct immunological screening (without using probes) deprived certain claims of novelty. The Opposition Division also took the view that certain technical terms used in the claims were not sufficiently clear at the filing date of the application, namely 'hybridize' and 'polypeptide of the IFN-α type'. Also the term 'degenerate' had not been correctly used in the claim. It is difficult to summarize the long argumentation on these points but the patentee was treated very severely on difficult points of terminology which fundamentally affected most of the broader claims.

Many more objections were raised in this case but fortunately it is unnecessary to discuss them because the decision has been very recently overturned by the Appeal Board. At this stage Biogen have good reason to believe that their patent will finally be vindicated in Europe.

One final aspect of this case must be noted because of its general importance to research workers who are prepared to take out patents for their discoveries but who are at the same time anxious to publish their work in the scientific literature. The issues involved in this question were discussed in the previous review and do not need repeating here. To recapitulate, however, in order to obtain patents in most countries it is necessary to file the patent application before the invention is disclosed to the public in any way. The United States and certain other important countries have what is known as a grace period provision which allows an invention to be patented after publication so long as the application is filed within a specified period, e.g. within one year for the USA. Although the safety-first policy of filing first and publishing second will in general enable the inventor to have the best of both worlds, a special problem arises in relation to a developing line of research where success comes finally only after a series of incremental steps. A patent application can be filed for each of these developments, one by one, and each of these will establish a so-called priority date for what it describes. A series of such patent applications, if their filing dates are all spanned within one year, may be combined into a single omnibus application. It often happens, however, that what is claimed in the final omnibus application cannot be found in its entirety in any of the preceding priority applications. There is the danger, therefore, that if the inventor publishes these developments as they occur, i.e. soon after the relevant patent application has been filed, one or other of these publications might be considered self-defeating prior art against the claim which is finally presented. Academic research workers will no doubt find this conclusion hard to swallow and this writer regards this as an unfortunate facet of patent law which we could well do without. Biogen had adopted this publication policy by publishing the contents of each of their priority applications shortly after these had been filed . As a result of this, the Opposition Division found some of the Biogen claims not entitled to the earlier priority dates and therefore to be lacking in novelty or inventive step over Biogen's own intervening publications. It is not yet clear what the final result will be on this aspect of the Biogen case.

To conclude this section of the review, a short account will be given of an important US court decision on a patent involving the use of monoclonal antibodies. First, certain background principles require discussion. In hybridoma technology the patenting of hybridomas and other cell lines is based on the principles established for micro-organism patents. Spleen cells (lymphocytes) taken from an experimental animal immunized with a particular antigen are fused with cells of a tumour cell line (myeloma) derived from an animal of the same or a related type, and from the resulting hybrid cells (hybridomas) there is selected the particular hybridoma clone which retains the property of selective antibody formation against a single particular antigen (monoclonal antibody). This hybridoma is itself a new cell line or clone. Inventions of this kind offer the possibility of claims to any novel parent myeloma utilized, claims to a family of derived hybridomas and to specific hybridomas, and claims to the production of monoclonal antibodies in process or product terms, as well as claims to applications of these in therapy or diagnostics. Many patents are being granted based on the use of monoclonal antibodies and systems containing them in diagnostic assays. In these the claims are directed either to the method of assay, or to particular reagent compositions or to combinations of materials useful in diagnostic kits.

After the publication in 1975 of the basic Milstein/Kohler technique and the subsequent appreciation of its more general importance, it was reasonable to assume that the patentability of any application of this general procedure must rest on some special and non-obvious property or advantage of the particular system constructed. In the previous review (Crespi, 1985) mention was made of the Wistar Institute case in which the following claim came under scrutiny:

> A process for producing viral antibodies comprising fusing a viral antibody producing cell and a myeloma cell to provide a fused cell hybrid, culturing said hybrid and collecting the viral antibodies.

In the UK the Patent Office took the view that since the basic monoclonal antibody technique had already been published it was obvious to apply this technique to an area where it had already been considered valuable, i.e. against viruses. The British Patent Office also would not allow a specific claim to the particular hybridoma developed for producing monoclonal antibodies against influenza virus. The applicant had not shown that the preparation of hybridomas of this type required anything other than the application of known techniques and, moreover, none of the hybridomas could be said to have particularly unusual advantages. It must be pointed out, however, that the US Patent Office did not take the same approach and in fact granted US patent 4,196,265 containing this broad process claim.

The Hybritech case

Hybritech successfully sued a number of companies under its US patent

4,376,110. The invention lay in the use of monoclonal antibodies in place of prior art polyclonal antibodies in a known sandwich assay system. When the US Patent Office originally examined the application it argued that it would be obvious to use monoclonal antibodies in place of polyclonals in conventional immunoassay protocols. This objection was overcome by including in the claims a numerical limitation regarding the affinity (binding power) of the antibodies. In the District Court the patent was held invalid on the grounds of obviousness, as many would have predicted, but this was overruled by the Court of Appeals for the Federal Circuit. Much of the case turned on aspects of US patent law relating to priority of invention which have no parallel in the patent laws of Europe and most other countries (*see* p. 255). Reference to laboratory notebooks and other evidence in order to determine priority of invention is crucial under the US first-to-invent system but is inadmissible under the European or any other first-to-file system of patent law. But on the question of inventiveness, the court upheld the patent because the prior art was 'devoid of any suggestion that monoclonal antibodies can be used in the same fashion as polyclonals'. Also, it was influenced by the commercial success of the patentee's product and found that a three-year time gap between the first availability of monoclonals and the sale of the patentee's kits was long enough to indicate lack of obviousness. The court also gave short shrift to the 'obvious to try' argument.

The decision given in this case (*Hybritech Inc. v. Monoclonal Antibodies Inc. 1986*) contrasts with that given by the British Patent Office, mentioned above, concerning the patent application for monoclonal antibodies to viruses. Although the subject matter was different in each case, the fundamental issue is one of the inventiveness or obviousness of particular applications of a recently discovered general technique. It should be remembered that decisions given in contested cases depend very much on the specific circumstances and the way the inventions are presented to the courts. Although courts are sometimes helped by experts, the problem of assessing complex technology and of making the difficult determination of inventiveness is acute.

CONCLUSIONS

From the few examples given above it is still too early to predict how the legal pattern will eventually be drawn. The climate for obtaining and defending US patents in this area certainly seems to be favourable. The European Patent Office also seems anxious to sustain biotechnology patents, at least at the Appeal Board level. The British t-PA decision, though apparently against the trend in the USA and Europe, supports the view that merely to be first in the race is not enough to stop all others from running along parallel paths that they have devised from the known and available technology. The British decision, it must be stressed, applies only to first-generation products. As regards next-generation products, numerous patent applications are now in the pipeline for modified or mutant forms of natural t-PA. It is clear that patent prospects are reasonable for these compounds. The new products show

structural variations in specific domains by modification or deletion of particular amino acids, e.g. in the growth factor domain, the kringle domain and the finger domain. Some modifications are devoid of carbohydrate structures at precise positions or have reduced glycosylation sites. These modifications are alleged to give improved properties, including longer *in vivo* half-life, greater affinity for fibrin or the fibrin/plasminogen complex, higher specific activity for the conversion of plasminogen, lower affinity for protease inhibitors and other desirable properties. Patent applications are also being directed to hybrid molecules containing part of the t-PA molecule combined with part of a pro-urokinase, prothrombin or streptokinase molecule or other moiety. The patentability of these new products will depend entirely on whether the modifications proposed do, in fact, result in the improved properties claimed. This will not always be apparent from the patent specification itself and supporting expert evidence may be required in the course of official examination of these applications.

The lawsuits described above have dealt entirely with specifics. Many more cases will follow in future where the issues of novelty, inventiveness and sufficiency of description will arise for treatment in the particulars of each situation. It is appropriate now to turn to those more general issues of legal policy under which the very nature and scope of patent protection in biotechnology is currently under official scrutiny. The WIPO 'Suggested Solutions' (WIPO, 1988) and the European Commission Directive (1988) were mentioned briefly earlier. These two approaches have much in common. The EC Directive (1988) acknowledges its derivation from the WIPO initiative and adopts the principles of the suggested solutions and much of their text. The major unsettled policy issue that they address is one of plant patents and the interface between patent protection and plant variety protection for new plants produced by modern methods of biotechnology, notably plant genetic manipulation. To see these proposals in the proper perspective it will be helpful first to sketch in the background to the present legal situation.

The plant variety right

This system came into being in the middle of this century in response to the demands of plant breeders for a protective mechanism which would ensure to them a financial reward for the long and uncertain process of developing new varieties. Theoretically, the patent system might have been used to meet these demands but it was considered unsuited both to the technology of the breeding process and to the interests of the industry. It is an essential part of patent procedure for the inventor to supply a written specification of the new process or product being patented from which it can be reproducibly performed or obtained. Although patents for agricultural machinery (which can be exactly defined) are commonplace, it was felt unrealistic to try to describe breeding/selection processes by detailed written protocols. The industry was simply not ready for patents which required precise definition of the organisms used or the products derived from them.

Against this background, and because a plant is a self-reproducing entity that

can give rise to an indefinite number of descendants and quantity of consumption material (i.e. product, harvest or offspring), the legislators deliberately restricted the scope of plant variety protection. Thus the line was drawn by reference to *propagation* and the *intention* of the propagator of the new variety. The nature of the exclusive right was defined in terms of the production and sale of the reproductive material of the plant variety.

Systems of plant variety rights of the kind described above were created under the national laws of various countries. Also, an international convention governing them, the International Convention for the Protection of New Varieties of Plants (UPOV), was drawn up in 1961 and took effect in 1968. Article 5(1) of the UPOV Convention (1961) states the right as covering:

> the production for purposes of commercial marketing,
> the offering for sale,
> the marketing,
> of the reproductive or vegetative propagating material, as such, of the variety.

It follows from the definition that the right cannot prevent the saving of seed from a current crop for sowing in a later season (the 'farmer's privilege'). Also, apart from certain provisions relating to ornamental plants, it does not cover the production and sale of the end product (consumption material) of the new variety, e.g. the fruit or grain. Finally, as specified by Article 5(3), the right does not prevent the use of the protected variety as source material for the addition of further variation in order to create yet another variety unless commercial production of the latter requires the repeated use of the protected variety (the 'research exemption'). For the traditional plant breeder and the farmer or grower it was considered necessary to preserve these freedoms. The UPOV Convention also provides in Article 2(1) that any member state can provide patent protection or plant variety right protection, but not both, for the same botanical species or genus.

In seeking protection for a plant variety, the most important part of the process is concerned with the examination of the biological material itself on behalf of the public body responsible for granting or refusing the application. Extensive field trials are necessary to determine whether the variety meets the legal requirements of distinctiveness, uniformity and stability (DUS). It is also necessary for the breeder to supply an objective description of the new variety and to list its characteristics in a qualitative or quantitative way by means of which it is distinguished from previously known varieties. Incidentally, the animal breeding industry in Great Britain is now beginning to consider whether some similar system would be useful for novel animal breeds. Here, however, the DUS criteria might be inappropriate or more difficult to apply than in the case of plants. One can think of a plant variety as a 'description' to which a particular plant must conform within a range of defined characteristics. These characteristics may be regarded as to some extent similar to the component parts of a patent claim but the comparison should not be pressed too far.

Unlike the procedure described above, the process of obtaining patent

protection depends almost entirely upon examination of the written word. In the case of micro-organisms and other living matter it is usually necessary to deposit a culture of a new organism in an official culture collection but this is essentially as a supplement to the written specification, which may itself be insufficient as an 'enabling disclosure'. The prime function of the specification is to describe the invention so as to enable persons of ordinary skill in the art to reproduce the invention. In addition, the specification contains the patent claims which define the protected technology.

Plant variety protection is highly specific to the particular variety and its scope is limited by reference to the physical (propagating) material itself combined with the description of the variety given in the documentary grant of the rights. As the difference between the novel variety and prior known varieties may not be very great, the narrowness of the protection is reasonable and acceptable to the breeder. Another difference between plant variety rights and patent rights is that the former give no protection for enabling technology. Because the plant variety right protects only propagating material it does not cover process technology, i.e. any novel technique for the production of new varieties, especially where applicable to a wider range of plant materials than the individual variety of a particular species.

PATENT PROTECTION IN EUROPE

In Europe and many other countries agricultural processes and products (but not agricultural equipment) were considered in the past to be outside the realm of the patent law. The European Patent Convention of 1973, however, declared agriculture to be on the same footing as other industries as regards the criterion of 'industrial applicability' which is necessary to establish the patentability of any invention under European law (EPC, 1973). Thus Article 57 states that

> an invention shall be considered as susceptible of industrial application if it can be used in any kind of industry, including Agriculture.

Nevertheless, Article 53(b) of the Convention states that European patents shall *not* be granted in respect of

> 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.

This exclusion is said to be justified by the fact that new plant varieties are protectable under the plant variety right system. The European Patent Office have nevertheless allowed a patent with a claim to 'Propagating material for cultivated plants, treated with an oxime derivative according to (a specified) formula . . .' (Ciba–Geigy patent publication No. 10,588). The Technical Board of Appeals held (*Ceiba–Geigy 1983*) that Article 53(b) prohibited only the patenting of plants or their propagating material in the genetically fixed form of the plant variety. The Board stated:

> The skilled person understands the term 'plant varieties' to mean a multiplicity of plants which are largely the same in their characteristics and remain the same within specific tolerances after every propagation or every propagation cycle . . . Plant varieties in this sense are all cultivated varieties, clones, lines, strains and hybrids which can be grown in such a way that they are clearly distinguishable from other varieties, sufficiently homogeneous, and stable in their essential characteristics . . .

The Swiss Patent Office has been the first national Patent Office to declare that patents will be allowed for new plants provided the claims are not directed to individual varieties, i.e. are more general in scope. This enlightened approach is now spreading to other jurisdictions and is about to be confirmed in the European Patent Office.

As regards patent claims for varieties, it can be said that the descriptions typically used in applications for plant variety rights would, in general, be considered rather imprecise for the purposes of a patent claim. An illustration of this point is the claim at present under consideration by the Supreme Court of Canada in an appeal against the rejection of a patent application for an improved soya bean variety developed by cross-breeding and selection techniques (*Pioneer Hi-Bred Ltd 1988*). This claim reads:

> A variety of soybean plant characterised by having the following characteristics:
>
> Seeds:
>
> | | |
> |---|---|
> | Shape | Oblong |
> | Surface | Sometimes wrinkled |
> | Seed Coat Color | Medium yellow |
> | Seed Coat Luster | Shiny |
> | Hilum Color | Light gray |
> | Weight | 18–20 grams per 100 seeds |
> | Cotyledon Color | Yellow |
>
> and also, exhibiting longitudinal discoloration of the seed coat stemming from the hilum, visible in the event that the plant has experienced considerable environmental stress;
>
> Leaves:
>
> | | |
> |---|---|
> | Color | Medium green |
> | Shape | Ovate |
> | Plant Pubescence Color | Medium Gray |
> | Plant Height | 27–35 inches |
> | Plant type | With intermediate canopy, i.e. intermediate between slender and bushy |
> | Plant Habit | Indeterminate |

Pods:

Color	Brown
Set	Scattered
Flower Color	Purple
Hypocotyl Color	Purple
Lodging Score	2·0 to 30, on a scale of 1–5
Maturity Group	

said variety resembling the soybean variety Corsoy with respect to plant shape, seedling pigmentation and leaf characteristics and the variety Portage with respect to seed size, and the variety Altona with respect to seed shape, and the variety Hardome with respect to color of hilum; and is further characterised by being resistant to the fungus *Phytophthora megasperma* var *sojae* (Races 1 and 2).

Both the Canadian Patent Office and the Appeal Court had taken the view that cross-bred varieties do not fall within the terms 'manufacture' or 'composition of matter' as used in the definition of 'invention' in the Canadian Patents Act. The Supreme Court must now decide this question.

THE UNITED STATES LAW

By contrast, the United States, always the exception in any comparative description of patent law, has permitted patents to be granted on plant breeding methods and products as well as allowing protection for varieties under the form of legal right known as the Certificate of Variety Protection.

An example of the greater flexibility of the United States patent law on plant patents is the Hibberd case (ex-parte *Hibberd 1985*). To produce a maize seed having an unusually high content of free tryptophan, the patentees set up a number of maize tissue cultures in the presence of inhibitory levels of a tryptophan analogue, e.g. 5-methyl tryptophan, in order to select a stable analogue resistant cell line from which maize plants could be regenerated. The main claim of US patent 4,581,847 reads:

> A maize seed having an endogenous free tryptophan content of at least about one-tenth milligram per gram dry seed weight and capable of germinating into a plant capable of producing seed having an endogenous free tryptophan content of at least about one-tenth milligram per gram dry seed weight.

A claim of this form is truly remarkable. It is expressed in terms of the end result rather than the means of achieving it. Nevertheless, so long as the inventor has provided a disclosure which enables the skilled person to produce a plant having these desirable characteristics it seems that such a claim is acceptable in the US Patent Office. For such a patent to be allowed in Europe it would be possible to argue that the claim was not for a new variety. Alternatively the seed could be said to be the product of a microbiological process and therefore patentable under the second limb of Article 53(b).

Patents on plant genetic manipulation

Plant genetic manipulation poses a new situation which cannot be fully catered for under the plant variety right system. First, the methodology can be written down as a reproducible disclosure. Secondly it can be generally applicable to numerous varieties and species of plant, so that in appropriate circumstances one might want to present a claim such as:

> Plants of the species (or genus) X having resistance to pathogens of the type Y by virtue of the transferred gene Z.

Methods for the production of new plant types will be patentable as methods (processes) whether the approach is by the recombinant or non-recombinant route. The reagents and other tools of these methodologies will also be patentable, including the development of new vector systems and gene inserts and methods of transforming cells. Transformed plant cells should also be patentable as products. Inventions which solve the problems of regenerating whole plants from transformed plant cells must also be patentable. In particular, there will be no obstacle to the patenting of novel DNA sequences which give rise to useful properties when inserted into a plant chromosome or at some other site. In principle these patents should have the same legal effect as other patents for chemical compounds and should therefore extend to all compositions containing them and to all uses to which they are applied to exploit their properties. However, genes are not very like industrial chemical compounds which, when formulated into mixtures, are usually fairly readily detectable in significant quantities. When new genetic material is inserted into a plant genome it loses its separate identity considered as a chemical compound. Reliance may therefore have to be placed on genetic fingerprinting or techniques for detecting the property for which the gene is responsible in order to prove that the plant is an infringing plant.

When gene sequences are made and sold by biotechnology companies the question of exhaustion of rights calls for consideration. Where a patented product is put on the market by or with the consent of the patentee the patent rights on the product sold became exhausted, i.e. the patent restrictions can no longer be exerted on products which have been thus purchased. This is now established case law in the United States and especially in Europe, where it is seen by the highest authority as a support to the principle of free circulation of goods under the Treaty of Rome. The Community Patent Convention (CPC, 1975) provides in Article 32:

> The rights conferred by a Community patent shall not extend to acts concerning a product covered by that patent which are done within the territories of the Contracting States after that product has been put on the market in one of these States by the proprietor of the patent or with his express consent, unless there are grounds which, under Community law, would justify the extension to such acts of the rights conferred by the patent.

How this principle is to be applied to a product that can be propagated to produce unlimited quantities of descendant material remains to be seen.

THE EEC DRAFT DIRECTIVE

The European Commission's proposal for a Council Directive on the Legal Protection of Biotechnological Inventions (1988) has been reviewed more fully elsewhere (Crespi, 1989). The Directive itself consists of 21 Articles but these are preceded by a dissertation analysing the problems to be tackled and explaining the purpose of the initiative. For present purposes it may be more helpful to present a summary concentrating upon the key issues.

Problems of existing laws

The European Commission has adopted the conclusion of the OECD study (OECD, 1985) that 'there is no other field of technology where national patent laws vary on so many points as they do in biotechnology'. The first concern of the Commission is that 'the existing lack of uniformity of approach makes it impossible for companies to treat the Community as a single market'. The single market is of course the central dogma of Community philosophy and differences of law are perceived as creating barriers to trade which are incompatible with the concept of a unitary market. To regard a weak patent law in any country as a major obstacle to the marketing of products there may be to overstate the case, as few firms would leave such a country as a vacuum to be filled by their competitor's products. On the other hand, there can be little doubt that legal uniformity provides a better environment for business. The second most important motivation of the Directive is the thought that European patent law is inferior to the corresponding law of the United States and Japan and may therefore be less encouraging to innovation in biotechnology. The object of the Directive to 'allow inventors and investors in the Member States to benefit from patent protection as effective as that in the competitive markets of Japan and the United States of America', is greatly welcome. The Commission highlights five areas of particular concern:

1. The criteria for patentability of living matter, particularly in relation to the exclusion of discoveries from patent protection and also in view of the novelty requirement.
2. The scope of patent protection for living matter, in view of the fact that living matter is self-replicable and therefore causes problems in respect of further generations.
3. The effects of the exclusion from patentability of plant and animal varieties upon the patenting of micro-organisms or taxonomic units different from plant or animal varieties or upon the patenting of parts of plants or animal varieties or their uses.
4. The distinction between an 'essentially biological process' (not patentable) and a 'microbiological process' (patentable).
5. The problem of sufficiency of the patent disclosure where the written description is inadequate for living materials; the use of culture collections

as depositories to remedy this shortcoming and the duties and safeguards involved in making use of this facility.

Patentability of living matter

The Articles begin strongly with the call upon member states to ensure that their national patent laws comply with the Directive. The Commission intends to bring matters to a head and to end what has often seemed to observers to be an interminable debate on all of these issues. Article 2 announces the bedrock principle that an invention cannot be disqualified from patent protection solely because of the involvement of living matter. In fact this principle is now accepted in the great majority of the member states of the EEC and also of the European Patent Convention (EPC). The exceptions are those states that have only recently joined one or other of these groupings, including Spain, Portugal and Greece, and in these countries the restrictions on patentability apply mainly to product patents and not to process patents. However, these countries are committed to raising the level of patent protection to that found elsewhere in Europe, a prospect which is of even greater importance with regard to chemical product patents, and so this transitional problem must eventually disappear.

The plant patent issue

Article 3 declares that micro-organisms and biological classifications other than plant or animal varieties shall be considered patentable. Moreover, claims for classifications higher than varieties shall not be affected by any rights granted in respect of plant and animal varieties. This means that if inventor A has a patent for a new type of plant, inventor B cannot escape infringement of this patent by developing a new plant variety from the patented plant, assuming of course that the claims of the patent are broad enough to include the new variety. Unfortunately the Directive falters at this point by introducing a proviso that plants will not be patentable if 'produced by the non-patentable use of a previously known biotechnological process'. This proviso is not totally clear and may well be modified before the Directive is finalized. If the intention is to make the availability of product protection subject to consideration of the process used to make the product, there is scant support in law for this standpoint and it is liable to cause more uncertainty over the question of patentability than obtains at present.

Essentially biological processes

The next most important group of Articles are Articles 5–7 which deal with 'microbiological processes' and also, by inference, with 'essentially biological processes', the two expressions which appear in Article 53(b) discussed earlier. It is the second of these two terms which presents the greater difficulty. It is hard to know what the legislators intended by an 'essentially biological process' but various attempts have been made to explain this. The European Patent

Office takes the view that such a process is characterized by the absence of significant human technical intervention, but this interpretation still leaves much room for debate. The Commission's view is that if this human intervention consists in more than selecting an available biological material and letting it perform an inherent biological function under natural conditions it must come into the category of a patentable process. In a recent decision of the Technical Board of Appeal of the EPO (*Lubrizol Genetics Inc. 1989*) some light has been shed upon this problem. The application claimed a process in which 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 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 Board explained that 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. Although in a multi-step process each single step as such may be characterized as biological in a scientific sense, 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 operations 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 an important technological character. This particular patent application will therefore succeed on this ground but it still has to be examined for other issues, e.g. novelty and inventiveness.

Use of an invention for experimental purposes

The view that patents somehow interfere with scientific research is sometimes expressed. This is an important point for the scientific community and in order to correct this common misunderstanding it is worth dealing with this topic at some length. Anyone may freely use a patented invention for experimental purposes but we must be clear as to what acts come into the category of experimental use. The legal doctrine was originally developed through case law but in European patent law it has now become part of various statutes, for example in the Community Patent Convention (CPC, 1975) mentioned above in the section dealing with plant patents. In CPC Article 31(b), acts which are done 'for experimental purposes relating to the subject matter of the invention' do not infringe a patent. So far, this is plain common sense, since anyone must be allowed to test what a patent describes and claims if only for purposes of evaluation. One can go further and say that so long as the use is in the context of research and the pursuit of enquiry into the invention itself no question of infringement arises. This last statement must not be misunderstood. Thus, if the patented invention is an item of laboratory equipment it is no defence for

one to say that it is being used in a research laboratory if the apparatus is being used in the context of some other field of research. If, however the experimental use is carried out for profit or with a commercial objective in mind the British and United States Courts have, in certain circumstances, declined to hold this to be permitted experimental use. It follows that this is an area of law in which interpretations can vary as to what acts constitute experimental use. The Commission sees this as a particular problem in biotechnology whereby, by the introduction of variation, third parties may be able to build upon a previous inventor's foundation without due recompense unless a legal loophole is blocked. The Commission states that:

> If a patented biotechnological product is employed to produce an improvement over the previous product, such use may legitimately be regarded as experimental use. If the improved product is a biotechnological product which is self-replicating, the patented starting material need only be prepared once in small quantities. To obtain commercial amounts it would not be necessary to re-use the product enjoying patent protection or to find a new way of production, avoiding the direct use of the patented product, as would be the case, for example, with a patented chemical product unable to reproduce itself. Replication of the small amount obtained in the first 'experiment' with self-reproducing material would suffice.

The Commission deals with this problem by means of Article 10 of the Directive (EC, 1988), the text of which is worthy of reproduction in full, as follows:

> The use of a product protected by a patent comprising or consisting of genetic information to develop another such product or the use of a patented process to obtain such a product shall not be regarded as experimental for purposes of establishing patent infringement, if the developed product obtained from the experiments or its progeny in identical or differentiated form, is used for other than private or experimental purposes.

Thus, to test experimentally a patented micro-organism to see whether it has the properties claimed by the patentee is permissible under existing law. But the proposed Article would make it an infringement to derive, e.g. by mutation, an improved strain of the original organism for commercial purposes (rather than merely for scientific interest). Of course, if the developed product falls within the terms of the patent claim it must infringe. This provision must therefore apply to the case where the new product is not covered by the wording of the claim.

In spite of the real problem to which the Commission has drawn attention there could well be more than one view about the desirability of this provision. If this were to be applied too restrictively, it might be said to muzzle further research and would therefore not be universally supported. Moreover, it is doubtful whether research workers would willingly accept any restraint which

would inhibit research of this kind. There are also difficulties over the enforcement of such a provision and it is not clear what the legal mechanism would be to apply it in practice.

The question of experimental use under this Article is dealt with as an aspect of the law of infringement. There is, however, one other important situation in which it is also involved. When an applicant for a patent deposits biological material in a culture collection there is a period in which the rights of third parties to obtain samples of the deposit are subject to certain restrictions, one of which is that the sample must be used only for experimental purposes until such time as the patent is granted. Discussion of this aspect of experimental use will be postponed until micro-organism deposit procedure is dealt with later in this review.

Exhaustion of rights

The Doctrine of exhaustion of rights was mentioned earlier in connection with the Community Patent Convention. It is a long-established tradition of patent law that a purchaser of a patented product from the patentee is free to put the product to such use as is consistent with its purchase. Thus, if a chemical compound is patented as an insecticide, it goes without saying that anyone who buys the substance from the patentee, or another manufacturer licensed by the patentee, must be free to use it to kill insects. It is equally clear that the purchaser must also replenish his supplies by further purchases from the patentee or licensee and cannot manufacture the substance for himself. If the product is a machine, then the purchaser is allowed to repair the machine, for example, by replacing parts which are worn out as a result of use, but strictly speaking the law does not allow the purchaser effectively to reconstruct an entirely new machine. It is logically consistent with these principles to hold that the purchaser of a product which is self-replicable cannot be free to use the purchased product in order to propagate unlimited quantities of progeny material. In Article 11 of the Directive the Commission seeks to establish a rule which would prevent the traditional Doctrine of exhaustion from being applied absurdly to living matter. The point is particularly important in relation to plant propagating material. The Commission observes:

> The purpose of Article 11 is to establish this rule for patented living or self-replicable matter. Thus, the purchaser of, for example, patented barley may use his barley to make whisky without infringing the patent; the purchaser of patented malt or yeast, for example, may use these products to make beer without infringing the patent. Both uses involve a certain amount of multiplication (such as germination) of the product sold but such uses are clearly intended by the sale. Where patented self-replicating material is sold for purposes of propagation, for example seeds, the purchaser, usually a farmer, will have the right without patent infringement to use the products for the purpose for which he purchased such seeds, i.e. to grow a crop for harvesting even though such use unavoidably involves multiplication of his seeds. The patent rights would

> not be exhausted in respect of the use of the crop grown from the patented seeds as a source for the sale of new propagating material (seeds) as this would involve production for the purposes of selling the patented product itself.

The text of Article 11 requires some clarification and will not be reproduced here; suffice it to say that multiplication and propagation by the purchaser is to be allowed 'only where such acts are unavoidable for commercial uses other than multiplication and propagation'.

The immediately following Articles of the Directive deal with other aspects of the scope of protection of a patent involving 'matter containing genetic information', particularly as regards subsequent generations and derived materials. For reasons of space these topics will not be discussed in detail here.

Dependency licence for plant varieties

In Article 14 the Commission attempts to tackle the problem of the interface between patent law and the law of plant varieties. On the one hand, as we saw earlier, the Commission is anxious to support patents for plants so long as these are not directed to individual varieties [thereby falling foul of Article 53(b)]. On the other hand, it wants to preserve the existing freedom to develop a new variety from a previously protected variety, presumably because this privilege has been enjoyed for so long that it would be undesirable to abolish it. The Commission attempts to reconcile these opposing considerations by the principle of automatic licensing in appropriate circumstances. Article 14 therefore reads:

> If the holder of a plant breeders' right or a variety certificate can exploit or exercise his exclusive rights only by infringement of the rights attached to a prior national patent, a non-exclusive licence of right shall be accorded to the breeders' right holder to the extent necessary for the exploitation of such breeders' right where the variety protected represents a significant technical progress upon payment of reasonable royalties having regard to the nature of the patented invention and consistent with giving the proprietor of such patent due reward for the investment leading to and developing the invention.

Article 14 is modelled along the lines of a corresponding WIPO suggested solution. This proposal has come in for a great deal of criticism at the WIPO Geneva meetings on the Suggested Solutions both from official circles as well as from industry and other interested groups. The chief objection is that the concept of 'significant technical progress' is inappropriate where plant variety rights are concerned because it is not one of the essential criteria for the grant of plant variety rights. It is a concept used frequently under patent law in support of the patentability of new invention over prior art and especially over prior patented inventions. Those industrial firms that are investing substantial sums in plant genetic manipulation are not in any way attracted to the idea of

automatic licences. They would prefer such matters to be resolved by the ordinary process of commercial negotiation which seems to work satisfactorily on the whole. The idea that a patent owner can sit on his rights and effectively block technological developments is one of the myths that continue to hover over the subject of patents, but which do not correspond to the realities of the modern industrial and business world. However, this particular difference between the industrial and agricultural lobbies may have to be resolved more by political compromise than by strict appeal to law and logic.

Deposition of biological materials in culture collections

The complex subject of deposition of new strains of micro-organism in official culture collections as a supplement to the written patent description was discussed at length in the previous review (Crespi, 1985). A key to understanding the official viewpoint on deposition is the notion that the deposit is a part of the total patent disclosure and must therefore in principle be available together with the written patent description whenever and wherever the latter is published. Any regulation covering this subject must therefore extend to the procedure for deposit, the procedure for obtaining access to the deposited strain by third parties, and to the facility for re-deposit in certain circumstances. The question of deposit has become a major facet of patent law for biotechnology and has already proved its potential to generate a body of case law peculiar to itself and capable of extraordinary development. The topic is addressed in Articles 15 and 16 of the Directive (EC, 1988).

The need for Article 15 is especially acute because of the difference between US and Japanese patent law, which allow access to the deposited culture only after an enforceable right has been granted to the applicant, and the corresponding laws in European countries, which allow access to the deposited culture upon first publication of the European or national patent application. The drawbacks of the European law on this topic have been emphasized by industry from the very beginnings of the European Patent Convention itself and the efforts of interested circles to improve the law have continued unabated since that time. In June 1980 the European Patent Office allowed a compromise amendment to the relevant rule (Rule 28) of the Regulations by allowing applicants to opt for the use of the so-called 'independent expert solution'. Whereas Rule 28 originally allowed access to any person on first publication, the amendment enabled applicants to restrict access to officially approved experts in the period between first publication of the application and the final publication on grant of the patent. These experts act as intermediaries but cannot pass the obtained sample of the deposited cultures to the parties for whom they act (usually the applicant's competitors). For European patent applications the present situation is set out in paraphrased form in *Figure 1*.

The text of Article 15 is too long and formal for reproduction here and it will be more appropriate therefore to summarize its main points. It is modelled closely on the structure of Rule 28 and therefore can be viewed as a developed form of this rule updated to conform to modern requirements. It is concerned with inventions involving any 'micro-organism or other self-replicable matter

After a European patent application has been published a sample of the deposited culture can be obtained according to the following conditions.

WHILE THE APPLICATION IS PENDING:-

Any person can obtain a sample if he undertakes

a) NOT to make it* available to a third party

b) to use it* ONLY for experimental purposes

(* or a derived culture)

UNLESS the Applicant has opted to limit availability to an INDEPENDENT EXPERT nominated by the Requester. The independent expert is bound by conditions (a) and (b)

and is either approved by the Applicant

or on a LIST of experts nominated by the EPO;

IF THE APPLICATION IS REFUSED/WITHDRAWN	: conditions a) and b) cease
WHEN THE PATENT IS GRANTED	: condition b) ceases
WHEN THE PATENT LAPSES or EXPIRES	: condition a) ceases

Figure 1. Availability of deposited cultures (based on EPC Rule 28).

which is not available to the public and which cannot be described in a patent application in such a manner as to enable the invention to be carried out by a person skilled in the art'. For these the disclosure requirements must be met mainly by the following conditions:

1. The biological material must be deposited not later than the patent application date.
2. Particulars of the deposit and of the culture collection holding it, together with information on the characteristics of the material must be disclosed in the patent application.
3. So long as the patent application is proceeded with, the availability of the deposited material to others, including the independent experts, is subject to certain specified conditions (these are virtually the same as in present Rule 28, except as discussed later).

All the conditions included in Article 15 are extended also to any matter derived from the deposited matter (by culturing or any other way of replication) which still exhibits those characteristics of the deposited matter that are essential to or for carrying our the invention.

The European Commission's commentary on Article 15 states: 'Unless the issues of the time and conditions of release are satisfactorily resolved inventors will be tempted to refrain from disclosing their inventions, to the detriment of the public and of technical progress in this field . . .' and it presents the proposed Article as an improvement on the current provisions of EPC Rule 28, particularly as regards availability of the deposited material. In Article 15 3(a) (EC, 1988) all availability is subject to the condition in the opening words: 'Unless the application has been refused or withdrawn or is deemed to be withdrawn . . .' and this general precondition is most welcome. In the case of refusal or withdrawal of an application, the applicant should not be obliged to make the culture henceforth available to third parties.

Furthermore, Article 15 3(b)(ii) requires the undertaking to use the obtained sample only for experimental purposes to be made permanent except in a country where a patent application has been filed; in such a country the undertaking ceases upon grant of the patent. This wording is proposed as an alternative to the version preferred by industry, according to which samples would be available only to residents of a country in which the patent application has been filed. The industrial view is motivated by the understandable desire not to lose control of valuable biological material through distribution to parts of the world where it may be used without recompense, and no organization can afford to patent every biological invention in every country. This view ought to appeal also to institutional research organizations where the funds available for patenting are even more limited. Indeed, research workers are themselves now much more cautious than they once were over the supply of precious strains to all and sundry and they, too, may welcome this attempt to improve the situation as regards deposit requirements. However, the protection given by an undertaking to use the culture only for experimental purposes is questionable. For example, it is difficult to see how it could be enforced against persons in a country in which no patent application for the invention is ever filed. There would be no legal sanction against such persons in case of a breach of undertaking and no practical course open to the applicant in such circumstances.

There are other Articles of importance to industry in the Commission Directive which, for reasons of space, must be omitted from this review. It is appropriate at this point to turn now to the new deposit rules that will soon come into force for patent applications in the USA.

NEW US DEPOSIT RULES

The new deposit requirements of the US Patent Office have been the subject of a series of drafts published in order to attract public comment. These rules are now so near the point of finalization that it must be reasonably safe to comment on the last draft to appear. The new US rules (Federal Register, 1988) will

depart in some important respects from the corresponding ideas of the European Commission Directive (EC, 1988), which are themselves in the process of being finalized for promulgation as the norm throughout Europe. The two major differences relate to the time of deposit and the conditions for availability of the deposited culture to third parties.

It was previously a very common assumption for any patent application, whether in USA or elsewhere, which required a culture collection deposit, that the deposit should be made before the filing of the patent application so that the appropriate cross-reference could be made in the specification as originally filed or could be added to it fairly soon after filing. There could then be no disputing the completeness of the applicant's disclosure as of his filing date and, consequently, no disputing the applicant's claim to priority as of this same date. This virtual unanimity was broken, however, by a decision of the US Court of Appeals for the Federal Circuit (CAFC) on a case in which the patent application was inadvertently filed a few days before the deposit was lodged in the culture collection (In Re *Lundak 1985*). The Court held that Professor Lundak's cell line was in effect deposited in his own private culture collection before the application was filed and was transferred to a public and officially recognized depository (American Type Culture Collection) some days after filing. This transfer of the deposit to the ATCC therefore provided a permanent and more reliable means of assuring access to the cell line upon the grant of the patent. This was a liberal decision and also one of refreshing common sense but it does involve a small gap in logic in that there is no automatic certainty of the identity of the two deposits. In formulating the new rules the US Patent Office was obliged to follow the *Lundak* decision. There is, of course, nothing to stop an applicant from depositing the culture before filing the application, according to the older practice, but if this is not done the question will fall to be determined during the prosecution of the application. Thus the Patent Office Examiner will have to decide whether or not a deposit is essential, whereupon it can be made at any time up to the date on which the final fee is paid which will result in the grant of the patent. In this case the applicant must verify that what is actually deposited, perhaps some years after the application date, is the same organism as described in the patent application. This relatively relaxed approach will not suffice for patent applications in Europe and other countries which have rules of the now conventional type. Therefore, for the purposes of international patenting, a US applicant cannot afford to be influenced by the US rule in this respect.

The second important area of difference between the US and European approach is concerned with the furnishing of samples of the deposit to third parties. Under US practice no such samples can be furnished to third parties until the patent issues, apart from the one exception that the US Commissioner of Patents can determine otherwise in very special circumstances. During pendency of the application, therefore, the applicant has complete control over the culture. As soon as the patent is granted the position changes. Previously the US Patent Office would allow no restrictions whatsoever to be placed upon the supply of the deposited culture to third parties after grant of the patent. This position is confirmed in the new draft rule 1.207 which includes the statement that:

> all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of the patent.

Rather puzzlingly, however, this robust statement is subjected to the later qualification that:

> the depositor may require that samples of a deposited biological material shall be furnished only if the requesting party has agreed in writing, not to make the deposited biological material or any biological material derived therefrom available during the term of the patent to any third party without the written permission of the depositor, and to assume the burden of proof concerning compliance with the agreement.

In this quotation the expression 'derived therefrom' requires an explanation and one is, indeed, provided by the Patent Office in the statement that:

> any biological material shall be deemed to be derived from the deposited biological material if it is replicated from, or would not have been produced but for access to, the deposited biological material, provided that the derived matter still exhibits the essential characteristics of the deposited biological material.

In their commentary on the proposed new rules the US Patent Office make reference to the WIPO Suggested Solution dealing with restrictions on access to the deposited culture. They decline to have anything to do with the idea of an undertaking to use the culture only for experimental purposes. In the WIPO proposal this undertaking was intended to last until the patent expired. In Article 15 of the Commission Directive, however, as we saw above, the corresponding proposal has been modified. On this point, therefore, the US and European attitudes are not far apart. The US Patent Office nevertheless has some very pertinent comments on the problems of the experimental use exception to the law of patent infringement. Because of the uncertainty in the experimental use exception it was probably wise to avoid introducing it into an administrative rule, especially as it is not clear how such rules can be enforced without full-blooded litigation on the legal issue itself.

The subjects discussed so far in this review have covered ground that has been well trodden in the legal literature. Among these the plant patent issue has dominated more recent contributions whereas the related issue of animal patents has taken a lower profile. This situation is changing rapidly and calls for a brief introduction to set the scene for the next flurry of excitement in the patent legal world caused by the dawning potential of animal biotechnology.

The animal patent issue

The genetic manipulation of animals raises many more issues than those of the patent law. The question is highly emotive and the arguments consequently

tend to be fired from deeply entrenched positions based on either law or ethics. In the resulting confusion the question of patenting animals has not escaped criticism. Since patenting, as such, is an ethically neutral activity, it is possible that the opponents of animal patents include them as a target because patents supposedly encourage investment in the research that will produce novel animal breeds. The subject is well treated in the most recent of a series of OTA reports (Office of Technology Assessment, 1989) and was also included in a conference sponsored by ICDA in the European Parliament (International Coalition for Development Action, 1989). These two documents show contrasting styles and approaches to this subject. As to the legal issues it is again necessary to deal with the USA and Europe separately.

ANIMAL PATENTS IN THE USA

In the Chakrabarty case (*Diamond v. Chakrabarty 1980*) the US supreme court upheld a patent for a manipulated bacterium on the grounds that it was 'a non-naturally occurring manufacture or composition of matter, a product of human ingenuity . . .' and also 'a new bacterium with markedly different characteristics from any found in nature and one having the potential for significant utility'. The court also held that patents can be allowed for 'anything under the sun that is made by man'. This broad ruling was the basis for the grant of patents for organisms higher than bacteria and also for plants, as in the maize seed case discussed previously (ex-parte *Hibberd 1985*). Its extension to animal patents was only a matter of time, although not without official opposition, as in the oyster case (ex-parte *Allen 1987*). The claim in the Allen *et al.* application was to a polyploid Pacific oyster produced by a certain process of applying hydrostatic pressure to the zygotes. The Examiner had argued that the claim was to living matter controlled by laws of nature and not by man, and hence unpatentable. But the Board held that the Chakrabarty case had established that the sole issue was whether the subject matter was man-made as distinct from occurring naturally. The Board refused the claim on other grounds but the importance of the case lies in their rejection of the Examiner's argument mentioned above.

Following the Allen case, the US Patent and Trademark Office (USPTO) issued the statement that 'the Patent and Trademark Office now considers non-naturally occurring non-human multicellular living organisms, including animals, to be patentable subject matter within the scope of 35 U.S.C. 101'. In conformity with this policy the first US patent for a transgenic animal duly appeared. US patent 4,736,866, issued to the President and Fellows of Harvard College is popularly known as the oncomouse patent, although its claim is not limited to the mouse and covers 'a transgenic non-human mammal all of whose germ cells and somatic cells contain a recombinant activated oncogene sequence introduced into said mammal, or an ancestor of said mammal, at an embryonic stage'. This patent is licensed to the Dupont Co. which will market the oncomouse. In the Patent Office, therefore, the matter is settled for the forseeable future.

Animal varieties are grouped together with plant varieties in the exclusion from patentability under Article 53(b) of the EPC (1973) and also in the corresponding provisions of national patent laws throughout Europe and elsewhere. It has been noted above that this only excludes the patenting of plants in the 'genetically fixed form of the variety', whatever that may mean. In practice, this distinction may be fairly easy to apply by examining the patent claim and deciding whether or not it looks like a typical description of a variety. This rather pragmatic approach is more difficult to apply to animals. First, there is no animal equivalent to plant variety protection under national laws or UPOV and therefore no comparable existing body of rules and experience governing the ways in which animal varieties can be characterized. Moreover, a genetically manipulated sheep programmed to secrete Factor IX in its milk may not look at all different from the parent animal from which the eggs were taken for micro-injection of the Factor IX gene construct. It would seem very difficult, therefore, for the European Patent Office (EPO) to refuse a patent for such an animal on the basis of Article 53(b). Patent applications can be refused under Article 53(a) if they are contrary to morality or '*ordre public*', the latter term apparently signifying anything calculated to cause a riot, for example. An objection to such a patent application under Article 53(a) would seem to be on very weak foundation. Nine applications claiming transgenic animals are currently being examined in the EPO (*see* Office of Technology Assessment, 1989, p. 23). Of these the oncomouse application may provide the anvil on which EPO policy will be forged. Almost certainly this will involve a decision of the Technical Board of Appeal, perhaps even of an enlarged Board of Appeal, in view of the issue of public policy that is involved and the strong precedent that will be created throughout Europe.

The animal biotechnology industry in Europe is now beginning to mobilize towards a consensus, if one is possible, of what the industry itself requires. There is a commonality of interest throughout the industry but this has not yet consciously materialized and been expressed in an equally positive manner by animal producers from all parts of the industry. The possibility of calling for an 'animal UPOV' is also under consideration. Animal biotechnology may emerge as the next major area in which the constraints of the European patent law have to be assessed and perhaps relaxed, through the Commission Directive or otherwise.

Conflict between publication and patenting

This concluding section of the review deals with a subject that is often problematical for research workers in biotechnology, in view of the strong incentive that exists in the scientific community to publicize discoveries of scientific importance at the earliest possible date. This tradition is common to the whole of science but in the biological field it amounts almost to a moral imperative in view of the potential of these discoveries to contribute to health, nutrition and human welfare. To achieve these benefits, however, it will usually be necessary for the discoveries to be commercialized, giving rise to

products that are made and sold to create profits from which further research may be funded. The patent dimension is therefore also important if all these aims are to be achieved. The research worker who wishes to secure both patent priority and scientific priority must follow the golden rule of filing a patent application before the corresponding scientific publication is actually published. The pressure for early scientific publication can sometimes give rise to problems in that the data intended for submission to the journal are insufficient to support a patent of suitable breadth to give effective protection which will cover further development by the inventor or by other research groups. But postponement of scientific publication may be unacceptable and there is therefore a resulting dilemma. This problem may in future be solved, or at least reduced, if the current WIPO proposals for a Harmonization Treaty are accepted and implemented world-wide.

The patentability of any invention depends critically on its novelty at the date on which an inventor has established his right of priority for patent purposes. For most countries, this date is the date of filing the patent application, the so-called priority date. This priority date is also relevant when a 'rival' inventor has applied to patent the same or a very similar invention. In such a competitive situation the patent will usually be granted to the first person to file an application which contains an effective disclosure. As explained in the previous review, the law in the USA is different from that elsewhere in that the date of filing of the application is not the sole deciding factor as regards previous publications (prior art) or the parallel claim of a rival inventor. US law also takes into account the actual date on which an inventor makes the invention, which can be established in some way, e.g. by laboratory notebook evidence. Thus the US system is described as a 'first-to-invent' rather than a 'first-to-file' system. However, to take advantage of this feature of US law an inventor must have made the invention in the USA, or introduced it into the USA, by the date in question. Therefore, the US system works in favour of the US resident inventor against the foreign inventor whose laboratory notebooks in his own country are disqualified as evidence of invention date unless they have been transported to the US and witnessed there.

A US inventor faced with a relevant publication by another person, which appeared in print before the inventor filed a patent application, can overcome it as prior art by showing that his invention ante-dates the publication. This is done by means of a formal declaration or sworn statement by the inventor, supported by documentary evidence. There is, however, a limit to the extent to which an inventor can use this facility to 'swear back of' a prior publication because if the publication is dated more than one year before the patent application date, it has a deadly effect under another provision of the law. A simplified statement of the US law relevant to this particular question is that the novelty requirement is met so long as the invention was:

(a)	not known or used by others in USA	before the
	or	applicant's
	not described in a printed publication	invention date

and

(b) not described in a printed publication / or / not in public use or on sale in the USA — more than 1 year before the applicant's US filing date

It follows from these two provisions that US law offers a 'grace period' of one year to any inventor, irrespective of nationality or location, as regards the inventor's own publication. The inventor may therefore publish the work and file within one year for protection in the USA. Canada has a similar grace period and a few other countries have a special 6-month grace period for certain special kinds of publication which will not be discussed in detail here.

The US system may appeal to those who feel it only right that a patent be awarded to the first inventor. However, US law considers that invention is a combination of conception and reduction to practice and, as these two parts of the inventive act are often separated in time, a great deal of case law has been generated relating to the determination of priority as between two or more conflicting patent applications. The first-to-file system, on the other hand, is simpler to administer; moreover it corresponds to the scientific tradition, which gives recognition to the person who is first to have the work accepted for publication rather than the first to make the discovery.

At the WIPO meetings preparing the ground for a possible treaty on the harmonization of patent law, representatives of the US Patent Office have appeared ready to seek for a change-over to a first-to-file system under their national law. This cause would not be promoted in isolation, however, and would have to be part of a total harmonization package that would justify such a major change from long-standing tradition. The US authorities are, nevertheless, intent on preserving the grace period provision. Although the grace period provision seems to be closely connected with the first-to-invent system, the two can be separated without difficulty. In their turn, the first-to-file countries now seem willing to accept the introduction of a grace period into their own laws. This would therefore be a major step forward in harmonization policy and would no doubt be welcomed by research workers of whatever disposition, academic or industrial.

The wording of the proposed grace period provision in a harmonization treaty remains to be settled. It will be to the effect that a patent shall not be refused or held invalid as a result of the public disclosure of information by the inventor or by a third party who obtained this information directly or indirectly from the inventor. It will apply also to co-inventors and any employing organization. The effect of this provision will be that an inventor's own publication within the preceding 12 months from filing will simply not be counted as prior art against the inventor, although it will count as prior art against rival inventors. However, depending on how this provision is finally worded, it may not be entirely foolproof for an inventor who takes advantage of it. As the publication itself will not convey any legal rights, there may be nothing to stop third parties, after reading the publication, from deciding to commercialize the invention on their own behalf in the period before the

inventor eventually files the patent application. Moreover, any such third party rights established in this way might be allowed to continue even after the patent application is filed. Until these matters are clarified, and national laws are changed, impulsive authors of scientific papers would do well to remember the golden rule: to file patent applications before any publication.

References

LITERATURE REFERENCES

ASSOCIATION FOR THE PROTECTION OF INDUSTRIAL PROPERTY (1988). *Resolution on Question 93*. AIPPI, Sydney.

BENT, S.A., SCHWAAB, R.L., CONLIN, D.G. AND JEFFERY, D.D. (1987). *Intellectual Property Rights in Biotechnology Worldwide*. Macmillan, London.

CRESPI, R. S. (1985). Microbiological Inventions and the Patent Law—the International Dimension. In *Biotechnology and Genetic Engineering Reviews* (G. E. Russell, Ed.), volume 3, pp. 1–37. Intercept, Newcastle upon Tyne.

CRESPI, R. S. (1989). The EC's proposals on the legal protection of biotechnological inventions. *Intellectual Property in Business* **1**(2), 2.

EUROPEAN COMMISSION (EC) (1988). *Proposal for a Directive on the Legal Protection of Biotechnological Inventions*. Communication 496 final SYN 159, Brussels 17 October.

FEDERAL REGISTER (1988). *Deposit of Biological Materials for Patent Purposes—Proposed Rules*. US Department of Commerce Federal Register, volume 53, No. 194.

INTERNATIONAL COALITION FOR DEVELOPMENT ACTION (1989). *Patenting Life Forms in Europe*. ICDA/GRAEL Conference, EP, 7–8 February, in press.

OFFICE OF TECHNOLOGY ASSESSMENT (1989). *New Developments in Biotechnology: Patenting Life*. US Congress Special Report OTA–BA–370, Washington DC.

ORGANIZATION FOR ECONOMIC COOPERATION AND DEVELOPMENT (1985). *Biotechnology and Patent Protection—An International Review*. OECD, Paris.

WORLD INTELLECTUAL PROPERTY ORGANIZATION (1988). *Industrial Property Protection of Biotechnological Inventions*. Documents BioT/CE/IV/2 and 3. WIPO, Geneva.

PATENT CASES CITED

Canadian cases	*Reported in Canadian Patent Reporter (CPR)*	
	Pioneer Hi-Bred	14 CPR (3d) 491
European cases	*Reported in EPO Official Journal*	
	Ciba–Geigy	EP00J 3/1984, 1/2
	Lubrizol Genetics Inc.	EP00J 320/87, in press
US cases	*Reported in United States Patent Quarterly (USPQ)*	
	Ex-parte Allen	2 USPQ (2d) 1425
	Diamond v. Chakrabarty	206 USPQ 193
	Ex-parte Hibberd	227 USPQ 443
	Hybritech Inc. v. Monoclonal Antibodies Inc.	231 USPQ 81
	In Re Lundak	227 USPQ 90

INTERNATIONAL CONVENTIONS

CPC (1975). *Convention for the European Patent for the Common Market.* For text see *Official Journal of the European Communities*, volume 19, no. 217, 26 January 1976.

EPC (1973). *Convention on the Grant of European Patents* (4th edn, July 1977). European Patent Office, Munich.

UPOV (1961). *International Convention for the Protection of New Varieties of Plants.* UPOV, Geneva 1982.