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Microbiological Inventions and the Patent Law—the International Dimension

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Introduction

Unlike most papers which appear in this series to review the state of the art, this contribution reviews the state of the law. It is focused narrowly, however, on the Patent law, one particular species of the legal genus of 'Industrial Property' which covers also Trademarks, Designs, Plant Variety Rights and Copyright. The law of industrial property, both national and international, is controlled by written statutes as well as court-made case law and sets down what sorts of invention and innovation may be protected and the procedure by which the appropriate protection may be secured. As against protection by means of patents, there has to be set the option of industrial or trade secrecy, the main broad alternative method of ensuring protection against piracy or imitation of ideas and valuable new technology.

Although the microbiological inventor may not expect to have a special patent law for his subject, he might well assume that this technology would be treated in much the same way by patent law from one country to another. He will be surprised by the diversity that exists among the different national systems and the variety of attitudes towards what may, or may not, be patentable. In the law of the European patent, for example, 'programs for computers' are specifically excluded from patentability. In contrast, the patentability of micro-organisms and other lower life forms is not expressly allowed or denied in any patent statute, yet the prejudice against patenting organisms has existed for many years and still survives in various parts of the world.

Biotechnology is rooted in classical microbiology, for which trade secrecy has often provided sufficient protection for the industrial innovator, but in its modern phase biotechnology has extended into areas in which patent

Abbreviations: CCPA, Court of Customs and Patent Appeals; EPC, European Patent Convention; EPO, European Patent Office; IDA, International Depositary Authority; NRDC, National Research Development Corporation; NRRL, Agricultural Research Service Culture Collection; RPC, Reports of Patent Design and Trademark Cases; UPOV, International Convention for Protection of New Varieties of Plants; WIPO, World Intellectual Property Organization.

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protection can make a significant contribution to scientific and business enterprise. Scientists and businessmen have accordingly looked to the patent law to provide forms of protection properly geared to the emerging ideas, processes and products of this new technology. But the patent law also has its traditions and these pre-date the newer biotechnology by a considerable margin. Moreover, patent law is based on general concepts which are required to apply to the whole range of inventions—chemical, mechanical, electrical, etc.—which come within its purview and therefore the microbiological invention must be fitted into this established conceptual framework as best it can. Although there is no separate patent statute law governing what is patentable in microbiology, there are special official regulations governing procedural matters for the patenting of microbiological inventions, e.g. the deposition of new strains in Culture Collections for patent purposes, and there is an international Convention which deals with this particular problem. There is also a substantial volume of case law on the subject, which will be outlined below.

The present state of the patent law can be best understood by tracing its evolutionary history. Before doing so, however, certain basic concepts must be clarified which are vital to an understanding of the current debate about the adequacy or otherwise of the patent law in relation to the more recent developments in biotechnology.

THE NATURE OF PATENTS

A patent is a form of property right granted by appropriate state authority in respect of an invention and legally enforceable by its owner against unauthorized exploitation by others. To obtain patent protection an application must be made to the Patent Office and this is usually done by the inventor or whoever claims the ownership and benefit of the invention. The patent application will be officially examined and, after a process of negotiation between the applicant and the Patent Office Examiner, it will be accepted or rejected. This examination is principally concerned with the written specification of the invention, which must be filed with the application and which must define the scope of the protection sought (the claims of the patent).

Among the criteria for patentability there are four basic requirements, three of which the invention itself must fulfil, namely, it must have (1) novelty, (2) inventiveness and (3) practical utility or industrial applicability while the other (4) concerns the specification; this must be adequate in content to enable those of ordinary skill and experience in the field to follow the directions and obtain the promised results. The application of these criteria in practice often involves legal subtleties, as will be described later, but they may be simply summarized as follows.

Novelty

This condition requires that the invention must not already be available to others by any kind of public disclosure or use before the date of filing of the

patent application. Although the rule is commonly expressed in terms of 'publication' it is important to note that this includes all forms of public disclosure and is not limited to literature publication. It covers *all* forms of publication, disclosure and use previous to the patent application, even those made by or due to the inventor himself! All such prior knowledge etc. is known as the 'state of the art' or 'prior art'. Prior experimental use which occurs within the privacy of the research laboratory is not part of the state of the art as long as the details remain as private or restricted information. A disclosure by an inventor can sometimes be confidential, as distinct from public, and this does not destroy novelty. This outline of the novelty rules applies to most countries; however, the United States, Canada, Japan and a few others are exceptions in allowing grace periods for filing patent applications in their respective countries after publication or use by the inventor.

Inventiveness

The invention must not be 'obvious' to the ordinary skilled worker over the state of the art, i.e. it must not follow plainly or logically from what is already known. Research workers who write literature publications which present their work as a natural logical scientific development from prior published papers make it difficult for themselves to argue that it has inventive character.

Utility or industrial application

Utility is a crucial concept in US patent law but is not limited to industrial utility and any other sort of practical utility can suffice. In European law an invention must be capable of industrial application.

Adequate disclosure

The description of the invention must be such as to permit repetition of the work by a person of normal skill. This criterion has led to special problems with biological inventions in that it is often difficult, or even impossible, to define living organisms or their products with sufficient precision to ensure reproducibility. This review will describe some of the changes which have taken place in the interpretation of patent law in response to a growing realization of these important features of patents concerned with biotechnology.

These four criteria can be interpreted in different ways by the different national patent authorities and may have to be conformed to meet new requirements or modified in the light of the findings of courts of law. For such reasons there are differences in patent law and its interpretation in various countries although international agreements have done much to minimize these inconsistencies.

SCOPE AND TYPES OF PROTECTION

A patent confers a monopoly without establishing of itself a situation which can be described as Monopoly. That is, a patent provides an exclusive right to the use and enjoyment of a *particular* invention. It does not monopolize anything more than the specific invention, does not preclude alternative and different methods of solving the same problem, and is not anti-competitive but on the contrary stimulates competition and the search for ways to 'design around' the patent. It is therefore a reasonable right to allow to those who invent and thereby enrich the state of the art. Moreover, the right is conditional upon any prior and wider embracing rights which may be held by others and is therefore not an automatic guarantee of the freedom to use one's own invention. The precise extent of the right in technological terms is governed by the patent claims, a topic to be discussed below. The writing of a patent specification is always a highly individual work tailored to the particular invention and the experimental data available but inevitably a certain stereotype structure acceptable to Patent Offices has emerged over many years. It is standard practice:

1. To state the problem at which the research has been aimed;
2. To discuss and assess previous attempts to solve it;
3. To describe the novel particular solution in broadest terms;
4. To provide data and worked Examples to instruct the reader how to apply the invention in practice. (The extent to which the invention is exemplified by actual data covering a wide range of possible application is crucial in determining the scope of the claims that will be granted), and
5. To present claims defining the scope of protection sought.

Patent claims

The claims of a patent have a purely legal function and although this is not precisely the same under all national patent systems it is broadly true that the wording of the claims is a guide to the scope of protection obtained. It is for the applicant to devise these claims and to do so wisely in order to cover all conceivable methods, forms and embodiments in which the invention can be exploited commercially. If this is not done comprehensively, the patentee cannot assume that a court of law will subsequently fill in for him the gaps he may have left in his protection inadvertently or through lack of foresight. Thus, in an early case about a patent for the manufacture of a cordite-like composition on which the inventor (Nobel) had sued an infringer, a British court pointed to the importance of the invention as *claimed*—'not the invention which the patentee might have claimed if he had been well advised or bolder but that which he has in fact and substance claimed on a fair construction of the specification'. Nowadays there is more latitude in the interpretation of patent claims but liberality cannot be taken for granted. Therefore the applicant, usually through his patent agent, argues the case with the Patent Office Examiner, and strives for allowance of the broadest possible claims and the greatest variety of claim types in order that his

interests are properly protected. In this the applicant does not have unlimited freedom, however, because the claims must be 'supported by the description' and therefore the experimental data and technical teaching in the specification provide some check on how many different types of claim can be obtained and what their scope may be. The famous Chakrabarty case decided by the United States Supreme Court in 1980 was essentially about what can properly be the subject of a patent claim in the domain of lower life forms.

Types of claim. The types of claim open to the applicant in relation to microbiological inventions will be discussed in detail later but for the present it will be sufficient to indicate their general character. The most usual forms of claim in microbiology are claims to new processes, products, compositions and uses. These are written in the form now well established for chemical inventions. Indeed, there is a considerable body of precedent in the case law of chemical patents that is taken over into its microbiological counterpart. Some of this will have to be mentioned below as background to our main focus of interest.

The product claim. This is of pre-eminent importance. Product claims are of two main types, known as the product *per se* claim and the product-by-process claim. A product *per se* claim is one that extends to a substance or micro-organism as such and is independent of any defined process of preparation or derivation. Such a claim is said to provide absolute product protection. A product-by-process claim, on the other hand, defines a substance or micro-organism in terms of some particular method of production. Hence the product-by-process claim is of more limited scope than the *per se* claim and can be avoided by the use of a production method differing from that defined in the claim.

Absolute product protection. This is available only where the product is a new substance, i.e. not disclosed or available to others by any kind of public disclosure or use before the date of filing of the patent application. Thus, prior written or oral disclosure of a compound, or indeed any other invention, and any other method of making the knowledge available in a public manner before seeking patent protection makes it part of what is termed the 'prior art'.

The product-by-process claim. This is used primarily where the novelty lies in the process, the product itself being known from earlier work and obtained by some previous process. Sometimes this form of claim has to be used when the product is in fact new but is of such complex and imperfectly known constitution that it cannot be adequately characterized in a product *per se* claim. Difficulties of this kind arose when the first attempts were made to patent enzymes and other large molecules including those produced by other technology, e.g. synthetic polymer chemistry. Definition of a substance in terms of biological function alone was usually not accepted by Patent Office Examiners conditioned by many years of experience with inventions in the field of simpler organic chemistry.

The discovery of biologically useful properties in a substance already known in itself. This could often be protected by means of a claim to a composition in which the known substance is present as an active ingredient, e.g. a pharmaceutical or insecticidal composition. An alternative to claiming the composition might be to claim the actual new use of the known substance, but this could not be done if the use was medical because of the specific exclusion of medical treatment patents in most countries (USA being the most notable exception). A further drawback to the use claim would be that, generally, the direct infringer of the claim would be the doctor, farmer or other end user, and legal action against these would not usually be worth while or desirable. For the patentee, the real target is always the commercial promoter or inducer of the infringement.

New methods of various kinds. These comprise another noteworthy group of inventions in the context of patent claims. Thus a method of treatment or processing of an industrial material is clearly an acceptable form of claim, as is also a claim to a method of testing where the method can be seen as applicable to manufacture in some way. Methods of assay were considered of uncertain patentability some 20 years ago, or it was thought slightly unethical to patent them, but these are now regularly patented and successfully licensed or otherwise exploited in the developing field of diagnostics.

Depending on where the novelty of the invention resides, therefore, the patenting strategy is to secure claims of the kind which give the patentee the greatest manœuvrability against those who might invade his lawful territory. This strategy is in some countries constrained by the fact that the relevant national law refuses in principle to allow product-*per se* claims and offers only process protection or product-by-process claims, thereby forcing the applicant to investigate and claim alternative processes so that no obvious loophole will be left to his competitors.

This basic outline of the subject of patent claims should assist in the understanding of the case law to be discussed below. An illustrative selection of specific examples of claims found in chemical and biological patents of the classical type has been given by the author (Crespi, 1982).

Historical perspective

For Europe, October 1973 marks a point of departure from centuries-old patent law for, in that month, the European Patent Convention (EPC) was signed in Munich by 14 signatory states and has since been ratified by 11 of them. EPC provides for a single centralized process of prosecution of a patent application and the eventual grant of a European patent in any contracting state selected by the applicant. Its importance in the present context is that it was the first statute to take specific account of microbiological inventions involving new micro-organisms, and provided a model procedure which subsequently has been emulated in many of the national systems of patent law

in Europe, which continue to exist alongside the European (regional) system, and also by national systems outside Europe. In fact, EPC cannot claim complete originality on this point because a United States court had, three years earlier, laid down a similar procedure which is now established practice for patent applications in the USA (*see later*). It will be helpful to an understanding of legal thinking on inventions in the biological sciences, first to outline progress up to 1973 and then to examine subsequent developments. This method of study cannot be applied to the law of all countries but the development is particularly clear in the case of British law and exposes important issues which have arisen in other countries too. The major decisions and developments in United States, German and Japanese patent law must also be highlighted in order to appreciate the international dimension in the patenting of microbiological inventions.

In English law, the origin of the patent system is the Statute of Monopolies 1624. This was an abolitionist statute, banning all previous forms of monopoly granted by the Crown but making an exception in favour of any Letters Patent granted for the 'making of any manner of new manufactures within this realm'. It was succeeded by the first United States and French patent statutes towards the end of the eighteenth century, with most other European countries following suit from the middle of the nineteenth century onwards. British Commonwealth Countries modelled their patent laws on the British prototype.

Although these laws have been successively modernized up to present times, one characteristic feature of the original legislation was retained and survives to this day. This concerns the nature or type of invention which can be covered by a patent. Thus the English statute had defined it as a 'manner of new manufacture' and this archaic phrase remained as the definition of 'invention' contained in subsequent legislation until its final appearance in the UK Patents Act 1949, which has now given way to the Patents Act 1977. This definition continued to give rise to problems because of its restrictiveness. The term 'manufacture' was officially interpreted as relating to the sort of activity that takes place in a factory. Hence agricultural methods, for example, were held to be outside its scope and therefore unpatentable. Moreover, it was considered essential for there to be a 'vendible product' at the end of the claimed process and this gave rise to difficulties for inventions in other technologies too. This key phrase arose in 1942 in the case of *GEC's* application* in which the claim was directed to a 'method of extinguishing incendiary bombs' by applying a solution of known chemical reagents. It was held that a method or process is a manner of manufacture if it (a) results in the production of some vendible product or (b) improves or restores to its former condition a vendible product or (c) has the effect of preserving from deterioration some vendible product to which it is applied. Many other inventions involving living matter were also held excluded by the term

* Such British cases are reported in *Reports of Patent Design and Trademark Cases* and can be traced by their RPC reference. A list of selected British and other cases is given at the end of this review.

'manner (or kind) of manufacture' and a body of case law grew around this concept.

Another factor, not so much of the early laws but of the late nineteenth-century versions, concerned the written specification. This became of increasing importance in deciding the legal scope of the patent. Here the claims were of primary significance. However, the concept of a patent as a privilege granted in return for the disclosure of something new and of practical value meant that the specification should be sufficiently clear and detailed for the performance of the inventive process, or the preparation of the inventive product, by a worker of ordinary skill. Eventually, one of the grounds on which a patent would stand or fall in a court of law was that of 'sufficiency of description' and this has become a virtually universal feature of twentieth-century patent law. In Germany the courts stressed the same idea in terms of 'reproducibility', a term which although particularly apt for biological inventions is nevertheless used essentially in relation to the written description, and this alone.

BRITAIN AND THE COMMONWEALTH

In the British case law the main thrust of the 'manufacture' argument was felt in the agricultural field. A case reported in 1951 concerned an attempt by *Standard Oil Company* to protect 'a method of producing an improved tract of arable land' by application of a known hydrocarbon composition as a selective weed-killer. This application was rejected for lack of a vendible product directly related to the method defined. Thus the crop grown on the land could not be described as the product of the process. In addition, it was considered that the crop itself was not improved or preserved from deterioration by the treatment. Furthermore, neither the land, nor the land plus the crop, could be regarded as the product. In *Lenard's* application a claim to a 'method of offsetting disease in clove trees' by long pruning together with a sterilizing treatment was simply refused on the ground that agricultural or horticultural treatments were not within the Act. Similarly in the case of *N. V. Phillips' Gloeilampenfabriekens* application directed to a method of producing a new form of poinsettia by the use of a sequence of artificial long-day and short-day conditions of specific duration and temperature, the judge considered that the invention resided in drastically changing the climatic conditions, whereupon something inherent in the plant itself would result in the production of a new variety. The modification of conditions under which natural phenomena pursue their inevitable course was held not to be a method of manufacture. In contrast, in *Szuec's* application a method of pelletizing mushroom tissue was allowed because this was in the same class as the manufacture of yeasts or other micro-organisms and was not a natural phenomenon of the kind found in the Phillips case. Again, the actual steps of the process were typical factory procedures so that this application could be accepted. Another attempt to obtain method protection for producing improved soil was involved in the case of *Virginia Carolina Chemical Corporation's* application in which the method step involved treating the soil

with a known chemical substance discovered to have properties as a nematocide. This suffered the same fate as the Standard Oil case. An attempt by *American Chemical Paint Co.* to patent a method for obtaining raw cotton by treating the plant with a defoliant was rejected on the grounds that the treatment did not affect the cotton but only removed the leaves of the plant. The process therefore did not produce cotton free of contamination, but merely the conditions whereby such material could be cultivated. These illustrative examples show that the mental gymnastics involved in drawing a line between manufacture and non-manufacture and in the rigid application of the 'vendible product' test were becoming rather exacting.

By 1961, British Patent Office practice in relation to processes involving living matter had become established. This was stated in the *General Electric* case where the claim was to 'a process for artificially inducing heritable variations' in the properties of micro-organisms by subjecting the culture to a defined electrical shock treatment whereby mutant strains were produced. Thus, the Patent Office explained that they had allowed claims to processes for producing vaccines and other compositions which included the treatment of an animal as a preliminary step. In the case of lower forms of life, claims had been allowed for the cultivation and treatment of yeast and of moulds for antibiotic production. Certain patents had also been granted where the product of the process was a living substance, the justification being that such substances would be regarded by the ordinary person as something bought and sold and used like many other commodities. In the General Electric case, however, the mutation process did not in general lead to useful results in the context of manufacture. Only in one instance, the mutation of *lactic streptococcus* (*sic*) for cheese manufacture, was there a manufacturing application disclosed and this had been specifically claimed in an earlier patent. The other examples (*E. coli* and *Micrococcus candidus*) were of academic interest only.

In the face of the established 'manner of manufacture' tradition, a suitable test case had long been needed to break the mould in which British and Commonwealth patent law had become set. The turning point came with the decision of the *National Research Development Corporation* to contest the doctrine in the High Court of Australia. The particular invention involved was based on the discovery by R. L. Wain that certain substituted phenoxybutyric acids were converted into the corresponding toxic phenoxyacetic acids by means of β-oxidase enzymes present in certain common weeds, thus enabling the parent compounds to be used as selective herbicides. Many of the compounds found to function in this way were new and therefore could be protected strongly by a product patent; however, an important group were known compounds. For the latter, claims to 'selective herbicidal compositions' were presented and allowed without difficulty. It was considered important, however, also to protect the method of use, as in the following typical claim:

> A method for eradicating weeds from crop areas containing a growing crop selected from leguminous fodder crops of the genera *Trifolium* and *Medicago*, celery and parsnip which comprises applying to the crop

areas a herbicide of the class consisting of the ω-(2,4-dichlorophenoxy)-butyric and -caproic acids, their salts, esters, nitriles and amides.

Other method claims were also presented in which the crop was specified as lucerne or clover and the weeds were specified as charlock, creeping thistle and annual nettle. The Australian Patent Office had raised the usual objection and rejected these method claims on the basis of the GEC and Standard Oil cases decided under corresponding UK practice. The Australian High Court, after reviewing the entire legal history of this doctrine, considered it to be a mistake to limit ones' thinking to the making of tangible products by hand or machine, simply because the everyday word 'manufacture' covered such an idea. It would be folly to fetter the underlying principle of the patent system by means of an exact verbal formula of this kind. The better approach would be to concentrate upon the idea of the useful arts, as distinct from the fine arts, and the corresponding idea of value in the field of economic activity. Similarly, the writing-off of agricultural and horticultural processes as outside the area of patentability could not be supported as a generalization. The appeal was therefore upheld.

The success of the NRDC case had rapid consequences. It was followed in the same year (1960) in New Zealand in the case of *Swift & Co's* application in which the claim was for a method of meat tenderizing by injection of proteolytic enzymes into the circulatory system of the animal prior to slaughter, in order to distribute the tenderizing agents effectively (the prior art being pumped infusion of the enzyme into the carcass). The Patent Office rejection of this claim was taken to the Supreme Court of New Zealand which endorsed the enlightened approach of the Australian court and extended it to embrace 'biological or physiological' inventions, as well as those in the categories of agriculture and horticulture. The tenderizing invention was clearly a manner of manufacture as 'interpreted in relation to a modern world's ever expanding and increasing knowledge of science and technology'.

Later in 1960 the Swift case fell to be decided on the corresponding patent application in the UK where, in spite of the NRDC and Swift precedents elsewhere, it was necessary to take a '*certiorari*' appeal to the High Court. The court held that, there being no prior English High Court decisions on the point, the Australian and New Zealand decisions must at least have posed a doubt, and one which the British Patent Office should have resolved in favour of the applicants. The desirability of a homogeneous development of law in all countries was also given as reason for quashing the decision to reject the application. Although the 'manner of manufacture' doctrine was not expressly jettisoned by the court, the practical effect of the Swift case was that it ceased to be applied on anything like its former scale.

The 'manner of manufacture' doctrine had not been applied to reject claims to specific mutants of yeast and other industrially useful organisms and, from this time onward, claims to other types of organism began to appear. The crucial issue of whether a product claim to a new micro-organism could be valid seems never to have been contested very far in the UK. Some applicants proceeded cautiously and claimed new strains in some particular form, e.g.

freeze-dried or mixed with a maintenance medium, to avoid the issue but, with the spread of confidence, claims to new strains in undisguised form were presented and the British Patent Office simply accepted them. Some examples are:

868,621 : Yeast (ATCC 13601)
1,015,262 : BHK 21 cells (hamster kidney) plus culture medium
1,085,798 : *Salmonella dublin* (ATCC 15480) freeze-dried
1,090,794 : *E. coli* CN 5364
1,286,250 : Feline heterodiploid cell line, beyond 40th passage
1,292,803 : Marek's disease virus free of A antigen
1,300,391 : Human liver cell line CL 99
1,346,061 : *Fusarium graminearum* IMI 145425
1,436,573 : Chakrabarty pseudomonad (multiple plasmid)

An even earlier and perhaps more remarkable patent was one for the synthesis of new strains of micro-organism (UK 719,313, mainly process claims) which covered the parasexual breeding technique described by Pontecorvo and his colleagues.

This liberal practice continued for about 10 years. Then an important case was taken to the House of Lords upon a petition to revoke *American Cyanamid* UK patent 934853 covering a new antibiotic named porfiromycin and the process for preparing it. The process depended on the use of new strains of *Streptomyces verticillatus*, samples of which had been deposited with ATCC and identified in the specification. The case was concerned only with the question whether, under the UK law as it then existed (1971), it was necessary to deposit a new strain in a Culture Collection in addition to providing a written description of the strain in the patent specification. However one of the judges, in discussing the central question, remarked that 'the priceless strain, being something living, found in nature, cannot be patented'. This was an *obiter dictum* and therefore not legally binding, but it began to be quoted against applications claiming new strains of naturally occurring organisms. This objection was frequently overcome, however, and claims to isolates of naturally occurring micro-organisms were generally accepted. By this time Britain had wholeheartedly committed itself to participation in a new system of patent law for Europe in which specific provisions for microbiological inventions would be present. Britain also intended to harmonize its national law with the future European patent law and, in these circumstances, it was in no-one's interest to promote any major controversy during the last years of the old law.

CONTINENTAL EUROPE

In continental European countries, the equivalent to the British 'manner of manufacture' doctrine was the concept of technical character and industrial applicability. Of these, technical character was the dominant influence,

excluding not only purely scientific discoveries but also much of biological innovation in agriculture, plant and animal breeding, and medical treatment.

In Germany, for example, the necessity for an 'instruction for technical activity' within a field of technology required official interpretation. The German Patent Office considered that, for the purposes of the patent law, technology was limited to inanimate substances and objects and the application to these of the techniques of physics and chemistry. However, classical fermentation processes were considered patentable because the final product of such processes was inanimate.

It was not until the 1930s that agricultural cultivation processes and new plant varieties were considered suitable subject matter for patents in Germany. This widening of the range of patentability so as to embrace the true biological invention was put on a firmer footing, at least in principle, by the decision of the German Supreme Court in the celebrated *Red Dove* case in 1969. The invention was for the breeding of a large dove, with particularly beautiful red plumage and other desirable physical characteristics, by a defined process of cross-breeding. The German Patent Office had rejected the claim on the ground that the process was not technical and its repeatability questionable. The Supreme Court supported the Patent Office on the repeatability argument with the result that the application was, in fact, rejected. However, the Court overruled the technical character argument, finding no basis in the law for excluding the utilization of biological forces and phenomena. The decision therefore made patents available for biological inventions, subject to the requirement of reproducibility. However, because of the great difficulty of complying with this requirement, in a very high proportion of cases the Red Dove has had the paradoxical effect of closing a door that the decision appeared to have opened.

The German court had specifically considered the argument that the reproducibility requirement could be met by the fact that the product of the breeding method could be propagated and would maintain its desired characteristics. This argument was rejected, however, on the ground that the ability of the animal to propagate itself was not equivalent to providing a teaching which would enable the skilled worker to repeat the breeding method for himself. These developments have been reviewed in depth by German authors (Duttenhöfer, 1971; Beier, 1972).

UNITED STATES AND CANADA

United States patent law defines the subject matter eligible for patent protection in a way which has evolved through successive statutes into its current form (US Code Title 35 Section 101) as:

> any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof.

This does not spell out the meaning of the term 'new' but in Section 102 of the statute the novelty condition is defined by a rather complex formula. The most

pertinent parts of the formula for present purposes apply the test for novelty in the light of what, previously, was known or used by others, or patented or described in printed publications or put to public use or on sale. Entitlement to a patent is also accorded by Section 101 to 'whoever invents or discovers' something falling within the above definition and it is clear that, of these two terms, one or the other is more appropriate as a description of the innovative act for the particular categories listed. For the present discussion, the critical part of the definition is the phrase 'manufacture, or composition of matter'.

The patent usually considered to be the first US patent granted for a micro-organism is the Pasteur patent US 141,072 of July 22 1873, including the claim to 'yeast free from organic germs of disease, as an article of manufacture'. It may be surmised that the last few words of the claim were felt necessary to avoid covering the natural product. Between the Pasteur patent and the Chakrabarty patent allowed by the US Supreme Court in 1980 with a claim to a genetically manipulated strain of *Pseudomonas* (*see later*), there have been many cases involving the 'product of nature' problem. This subject has attracted the attention of many authorities including European writers (Utermann, 1978; White, 1980) who have discussed it internationally, and a much greater number of United States authors who have focused upon the particular legal problem in their own country (e.g. Wegner, 1976, 1978; Dunner and Lipsey, 1979; Biggart, 1981; Cooper, 1982a).

Of the many decisions bearing upon the patentability of natural products, the opposing strands of opinion can be seen from the following four cases. In *American Fruit Growers Inc.* v. *Brogdex Co.* in 1931 the US Supreme Court held a borax-impregnated orange unpatentable as a product of nature. The claim was in the form 'fresh citrus fruit of which the rind or skin carries borax in amount that is very small but sufficient to render the fruit resistant to blue mould decay'. Even though the borax-impregnated orange does not occur naturally, the prejudice against patenting such objects was expressed in the court's statement that the borax conferred no new distinctive form, quality or property on the fruit but merely protected it against deterioration: 'It remains a fresh orange fit only for the same beneficial uses as before'.

The important case of *Funk Bros. Seed Co.* v. *Kalo Inoculant Co.* decided in 1948 was one of the main precedents which figured in the Chakrabarty case and therefore deserves detailed attention. The invention was based on the discovery that there were certain strains of nitrogen-fixing rhizobia which were not mutually inhibitory and therefore could be combined into a mixed inoculant for legumes. In the prior art it was considered necessary to inoculate separately with single-strain inoculants to avoid the problem of inhibition. The actual non-inhibitory combinations discovered were rather limited in number but the patent contained the following broad claim, amounting virtually to a claim to the principle involved:

> an inoculant for leguminous plants comprising a plurality of selected mutually non-inhibitive strains of different species of bacteria of the genus *Rhizobium* such strains being unaffected by each other in respect

> to their ability to fix nitrogen in the leguminous plant for which they are specific.

The Supreme Court held this patent to be invalid because the qualities in the strains were the handiwork of nature and the mere aggregation of these strains was considered to produce nothing over and above the sum of their individual properties. Thus 'the bacteria involved performed in their natural way and their combination did not improve their natural function which was to serve the ends nature originally provided, independently of any effects by the patentee' (abbreviated quotation). As in the case of the borax-treated orange, the mixed inoculant culture claimed in the patent was not shown to occur in nature. Nevertheless, the natural occurrence of the main component or components of the claim seems to have influenced the court against what would appear to have been the strict logic of the situation.

The classic case in which a claim to a natural product was upheld is that of the vitamin B_{12} patent US 2,563,794, *Merck & Co. Inc.* v. *Olin Mathieson Chemical Corporation*. The vitamin occurs in liver, and certain liver extracts had been tried in the treatment of pernicious anaemia, but rather unsuccessfully. The patentees had produced B_{12} by fermentation of certain strains of *Streptomyces griseus* and this had led to the production of therapeutically useful quantities of the pure substance. The product claim defined the substance as 'the compound vitamin B_{12}. . . .' in terms of elemental analysis, solubility in certain solvents, spectral absorption data and a numerical specific activity. The properties recited in the list are, of course, inherent in the substance in whatever state it may be found or presented, but they are determinable only in the purified material. The patent was attacked on the ground that it claimed a product of nature which was merely a purified form of the natural substance. In rejecting this attack, the court relied on previous cases where the isolation of a natural product had effectively contributed a new utility to the art and they stated the principles as follows:

> The step from complete uselessness to great and perfected utility is a long one. That step is no mere advance in the degree of purity of a known product. From the natural fermentates which for this purpose were wholly useless and were not known to contain the desired activity in even the slightest degree, products of great therapeutic and commercial worth have been developed. The new products are not the same as the old but new and useful compositions entitled to the protection of the patent.
>
> Before Rickes and Wood made it available to the world, pure crystalline vitamin B_{12} as described and claimed in the '794 patent did not exist. No-one had produced even a comparable product. The new product had such advantages over the earlier liver extracts that it not only replaced them but became, and remains to this day, the universal treatment for pernicious anaemia.

Another important case was that of *Parke-Davis & Co* v. *H. D. Mulford Co.* in which a claim to adrenalin was vindicated. The claim was directed to a

substance possessing the 'physiological characteristics and reactions of the suprarenal glands in a stable and concentrated form and practically free from inert and associated gland tissue'. It was held that the inventor 'was the first to make it available for any use by removing it from the other gland tissue in which it was found and, while it is of course possible logically to call this a purification of the principle, it became for every practical purpose a new thing commercially and therapeutically'.

In the vitamin B_{12} case there was clear merit in making the substance available by fermentation but it is important to note that, in the adrenalin case, the process of production was by extraction from the natural source. Many natural products have to be produced by extraction rather than by synthesis, but this is not necessarily to depreciate the step forward which has been made in the art, and should in no way detract from patentability.

Canadian patent law has a definition of invention identical in wording to that of the US statute, although it recognizes precedents in British case law as well as those in US decisions. It was a long-standing official practice until 1972 to reject certain claims, process or product, with the stock objection that:

> Living organisms, ranging from the lower forms of life, such as viruses, bacteria and fungi, to the higher animals and plants are self-propagating entities and have evolved by processes of self-variation and reproduction which only the particular organism itself is capable of performing. They cannot therefore be regarded as products of human manufacture. In the live state, either alone or in association with inanimate material, they do not fall within the definition of invention according to Section 2(d). Since living plants and animals whether *per se* or in compositional form may not be patented, the more primitive forms of life, which share the same property of self-reproduction, are likewise unpatentable. Being manifestations of natural phenomena they lie outside the sphere of patent monopoly.

In October 1972 a change of policy was declared. In the writer's experience this occurred in connection with two NRDC patent applications in which an appeal was lodged against the Examiner's rejection of claims to pig and calf *Salmonella* vaccines comprising attenuated strains of *Salmonella cholerae-suis* and *Salmonella dublin* respectively, in association with a pharmaceutically acceptable carrier. At about the same time other applicants were also contesting the establishment view and there was therefore a strong case for reconsideration by the Patent Office. After the revision, 'processes and the products thereof in the microbiological field were not necessarily excluded from patentability'. It is important to note that claims to micro-organisms *per se* were not specifically in issue at that particular time.

JAPAN

It is often said that, when Japan began to industrialize in the early years of this century, it was influenced by the patent system of the United States of America which, the Japanese believed, was a contributory factor in the

remarkable economic progress made in America. However, in establishing its own system Japan was also influenced by German ideas of patent law. Thus an invention is defined as 'highly advanced creation of technical ideas by which a law of nature is utilized' and this concept can be traced back to German legal scholars. In practice it is the idea of technical content which has come into the foreground, together with industrial applicability, which is also a specific criterion in the Japanese statute. Furthermore, as in German thought, the technical content idea has become closely associated with the necessity for reproducibility of the teaching and this latter requirement has been stressed repeatedly.

The Japanese Patent Office is unique in its propensity for issuing guidelines for the patenting of inventions in various branches of technology. These are known as 'Examination Standards' and, again, some of this uniqueness lies in the readiness of the Patent Office to consult with industry and other users of the patent system in the preparation of such guidelines. Some commentators outside Japan suggest that the Examination Standards are over-detailed, require too much from the applicant and tend towards rigidity of practice. Whatever opinion one adopts, guidelines have the advantage that the applicant and inventor know from the beginning what sort of data will help their case.

In the 1950s, Japanese litigation on patents for chlortetracycline produced by *Streptomyces aureofaciens*, and other disputes about the identification of certain micro-organisms referred to in patents for the production of glutamic acid, led to a general realization in Japanese official circles and industry that clarification of nomenclature and the general procedure for the patenting of microbiological inventions was necessary. In 1965 the first Examination Standard for 'inventions concerning micro-organisms and the fermentation industry' was issued. In 1970 this was re-titled as a standard for the 'applied microbiological industry'.

Processes utilizing micro-organisms presented no difficulty over patentability. At that date, however, micro-organisms were officially regarded as unpatentable on the ground that they were not industrially applicable and also because the invention could not be reproduced (*sic*) 'in the same manner that plants and animals are not patentable'. This policy was reversed in a new guideline issued in 1979.

Patentability conditions: their impact on microbiology

Technical character and industrial applicability are not the only criteria for patentability of an invention. As noted earlier, the subject matter of the patent claims must also be both new and inventive when compared with the pre-existing state of the art ('prior art'). However, novelty is not conceived and formulated identically in all patent laws. In the European Patent Convention, for example, the novelty condition is expressed in a different form from that in which it is presented in the United States and Canadian statutes. As this review has so far followed a chronological approach, discussion of the legal concept of novelty will be postponed until the question

of the patentability of micro-organisms is dealt with. In the order in which they have more recently arisen as contentious issues in relation to microbiological inventions, novelty and inventiveness have given place to the major debate over the application of the fourth main criterion of patentability, namely, the adequacy of the patent specification as an instruction to the skilled worker for practical performance of the invention.

Adequacy of description

This requirement is usually expressed as sufficiency of disclosure, enabling disclosure, reproducible teaching, or in similar terms. The belief is sometimes stated by research workers that patents frequently do not fulfil this expectation, i.e. that they leave out something essential, either deliberately or through lack of appreciation on the part of writers of patent specifications. Whatever the extent to which this belief is justified, a patent must not be defective in this way if it is to stand up in court.

In mechanics, physics and classical organic chemistry it is usually possible to define an invention and to transfer adequate information to the skilled person by means of the patent specification. With complex biological material such as enzymes and cells, however, our knowledge and descriptive powers are often insufficient for this purpose. Not only does a complete description require massive amounts of data, but in addition the description must ensure the possibility of performance of the described procedure by the skilled worker in order to obtain the product or result, be it a new product or result, or a known one produced in some better way by the new process. Where a new micro-organism (i.e. one not already available to the public) is an essential element of the invention, and it cannot adequately be described or a repeatable method of obtaining it cannot be given, it was considered that the difficulty could be solved by depositing the new micro-organism in a Culture Collection which was sufficiently public in nature to provide an objective source of reference and supply. Patent practice on this expedient has given rise to a new dimension in the case law and statute law of patents over the last decade and more and deserves special attention in this review.

THE DEPOSITION OF MICRO-ORGANISMS IN CULTURE COLLECTIONS FOR PATENT PURPOSES

The first legal decision bearing upon this subject was given in 1970 by the United States Court of Customs and Patent Appeals (CCPA) *in re: Argoudelis*. However, bearing in mind the basic principle that a patent is granted to the inventor in return for the useful and usable new information he provides, the need for deposition and availability of the micro-organism had been realized intuitively much earlier and the practice of depositing strains had begun voluntarily from 1949 onwards in the United States and elsewhere (*see also* Chapter 13, page 431). The question immediately arises as to when a deposit should be made in the Culture Collection and when the culture should be made available to the public in the time-scale of patenting

procedure. Before practice became stereotyped there was some variation of thinking in this respect, but the prevailing view was that deposition of the micro-organism, before the filing of any patent application, was desirable and probably necessary in order to identify the strain in the specification as first filed. On the more controversial part of the question, i.e. on the release of the strain to third parties, a choice of three alternative dates must be made: the date of filing, the date of publication or the date of grant of the patent. It is clearly in the interests of the applicant to delay release of a new strain to competitors for as long as possible and at least until the grant of an enforceable right. In the USA, publication and grant of the patent occur at about the same time and this is, therefore, a convenient stage at which release of the deposited strain will meet the legitimate wishes of all parties. However, many other countries have adopted a dual publication system in which the unexamined application is published early, followed by a second publication of the finally accepted specification at the time of grant, and there has been disagreement as to which of these two dates should apply in such circumstances.

In the Argoudelis case the claimed inventions were two new antibiotics and a microbiological process for their production. The process was dependent on a new *Streptomyces* strain which had been isolated from nature and deposited, before the filing of the US Patent Application, with a public depository (the Agricultural Research Service Culture Collection, NRRL) in the USA. The micro-organism had been deposited under the condition that it would not be distributed to members of the public (other than applicant's nominees) before the patent was granted, at which time it could then become accessible to all. The US Patent Office had argued that this deposit was secret and confidential and therefore that the application was defective because the micro-organism had not been made available to the general public at the time of filing of the patent application. The Court held that there was no need for a micro-organism to be available at the time of filing the application. It was not necessary for the public to have access to the culture before issuance of the patent. The disclosure was 'sufficient to permit a thorough examination by the Patent Office and to preclude the possibility that a patent could issue without any person skilled in the art being henceforth enabled to make and use the invention'. The applicant had set up a procedure whereby, at the time the patent was issued, there would be no doubt that a person of ordinary skill would be able to make the claimed antibiotics with the critical micro-organism which would then be readily available to him.

The procedure laid down as acceptable in this case has long since been the established official practice in the United States and it commands wide assent. In the same year as the Argoudelis decision a similar point had arisen in Britain in the previously mentioned case of *American Cyanamid (Dann's)* patent and was taken to the House of Lords. It was held that the law existing at the time simply did not cover the situation. Thus the highest English Court did not define a pragmatic solution along the lines of the US decision but, in true common law fashion, declared a hiatus; all the law required was a written description. The court therefore refrained from devising a rule to cover the

situation. The German Supreme Court felt under no such inhibition, however, when a related point arose in the *Baker's Yeast* case in 1975. This case is of special importance on the patentability of micro-organisms, but its ruling on the date of public availability of the deposited culture has also been highly influential and still stands. In adopting the early publication date (first publication of the unexamined application) as the crucial date for availability of the culture to the public, the German court was no doubt influenced by the identical position taken in the European Patent Convention which had been signed two years previously. The issue involved here concerns the effectiveness of the patent specification as a publication and emphasizes the informational purpose of the patent system.

PUBLICATION AND PATENT PROCEDURES

To those who see a conflict between patenting and publishing, it must be pointed out that it is of the essence of patenting to involve publication, but through the official channel. Those whose only motivation is to achieve scientific priority by publishing in the journals, will find that this usually precludes subsequent patenting. However, the real incompatibility is between publication and a policy of total secrecy which will not tolerate even the publication which flows from the patenting process. In the past, and in most countries, this process resulted in publication of the specification only at the end of negotiation between applicant and Examiner, as it still does in the USA and Canada. However, many countries considered that long delays in disclosure of the information in patent specifications were against the public interest and so adopted a practice of publishing the application at an early date, even before its examination had begun, e.g. in Australia, Netherlands, Japan and Germany. This practice was taken over when the European patent law was created in 1973, and other countries have since followed suit, so that it is now common to find patent applications published at about 18 months after their own filing date or the filing date of an earlier application on which they rely for priority, as will now be explained.

An application for patent protection is normally first made in the country of residence or place of business of the applicant. This establishes a so-called priority date which will be recognized in most of the other countries of the world under the provisions of an international convention known as the Paris Convention. In practice this means that the major expense of a foreign patenting programme can be postponed until towards the end of one year after the initial filing date in the home country. For this purpose an application for a European (regional) patent is on the same footing as national applications in other countries filed under the Paris Convention. The value of this one-year interim period, both to industry and to other organizations which have the problem of assessing the potential industrial importance of new research results, is considerable. Between competing interests there is always a race to establish the earliest priority date, but this eagerness has to be tempered by the uncertain evaluation of the commercial prospects of the invention at such an early stage. The one-year breathing space offered by the

Paris Convention is of some help and focuses the minds of those engaged in research and development and also of those who authorize expenditure on patenting. *Figure 1* summarizes these procedural points. The other major advantage given by the Paris Convention is that the inventor can publish details of his invention at any time after his priority date without detriment to his patent prospects. The only provisos here are that the invention is clearly defined and well supported by data in the first application and that the foreign applications are filed no later than one year after the first application.

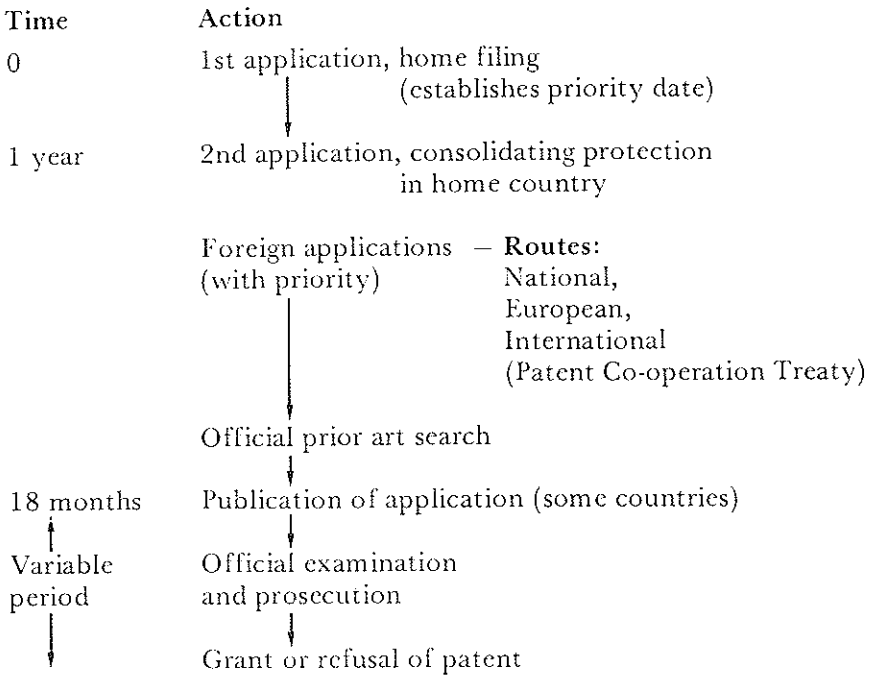

Figure 1. Patenting procedure.

THE EUROPEAN PATENT CONVENTION

Availability of novel organisms

The European Patent Convention (EPC) 1973 provided for the deposit of a new micro-organism in Rule 28 of the *Regulations*. This required an applicant to make the deposit in a Culture Collection not later than the European patent application date, to add to the application identifying details of the deposit, and to make the deposited micro-organism available from the Culture Collection to any person from the date of first publication of the patent application. The European Patent system had committed itself to a policy of dual publication of the kind mentioned above. The release of the

deposited strain at the 18-month stage, at which time there is no certainty of the grant of patent rights, was clearly controversial, but the majority official view prevailed and Rule 28 came into existence as the model for the subsequent amendment of National laws in Europe in harmony with the EPC.

A deposit under Rule 28 gave irrevocable consent to the availability of the deposited culture under the rule and this could be withdrawn only by abandoning the patent application before preparations for its early publication had been completed. Availability to third parties was subject to certain undertakings: while the patent application was pending, or as long as the eventual patent lasted, the culture could not be passed on to others by the third party; in addition, during the pendency of the application (but not after grant) the third party undertook to use the culture for experimental purposes only. Both conditions ceased upon refusal or withdrawal of an application. The identity of the person obtaining a sample would be communicated to the applicant.

THE BUDAPEST TREATY

The EPC was signed in October 1973 but did not come into operation until June 1978. Meanwhile, the need had been recognized in official circles to establish arrangements for deposition procedure which would be adopted on an international scale wider than the area embraced by the EPC signatory states. Under the auspices of the World Intellectual Property Organization (WIPO), preparations began in 1974 towards this objective. As a result, the 'Budapest Treaty on the International Recognition of the Deposit of Micro-organisms for the Purposes of Patent Procedure' was signed at Budapest in 1977 and entered into force three years later.

According to the Budapest Treaty, a Culture Collection may become designated as an International Depositary Authority (IDA) and thereby become recognized for the deposit of micro-organisms for the purposes of patent applications in any of the contracting states. A single such depositary, whatever its location, can therefore be chosen by an applicant to hold a deposit relevant to a single patent application or to a family of related patent applications filed in any number of contracting states.

The Budapest Treaty covers the formalities of deposit and maintenance of the culture and the possibility of re-deposit where the original deposited strain has lost viability upon storage. An IDA must store a deposited micro-organism for at least 5 years after the most recent request for the sample and for at least 30 years from the date of the original deposit. The procedure for release of samples of the deposited culture to various parties is covered in detail.

The amendment of EPC Rule 28

In June 1980 an amendment of Rule 28 was made to bring the original rule into alignment with the terminology and procedures of the Budapest Treaty. Further changes were made as an accommodation to the views of interested

circles which had maintained that the original rule was in certain respects too harsh to the applicant. This standpoint has been discussed by European workers (Hüni, 1977; Crespi, 1981, 1983).

The main target of criticism of the original Rule 28 was the requirement to make the deposited culture available to *any* person at the date of first application of the European patent application, i.e. at 18 months after the application date or priority date. At this date the applicant has no certain prospect of obtaining patent protection and no right of any kind which is then enforceable. The only protection the applicant has at this stage is that given by the above-mentioned undertakings of third parties. Furthermore, the predominant role of the micro-organism itself in producing the end-product of the microbiological process, and also the ease of replication of the micro-organism, combine to give an unfair advantage to competitors at such an early stage by physically putting into their hands the chief instrument of performing the process of the invention. A further problem arises from the relative ease with which micro-organisms can be modified, either by conventional mutagenic treatment or by direct chemical treatment of DNA molecules. These present the applicant with substantial problems of proof of derivation from the deposited strain. In any case the legal question of patent infringement by modification of deposited organisms is by no means clear and settled. The question of derivation, for example, must be decided by expert scientific evidence, which may be conflicting. In the case of *American Cyanamid* v. *Berk Pharmaceuticals*, on a process for producing tetracycline, there was contradictory evidence upon whether the strain used by the defendants was a *Streptomyces aureofaciens* of the kind claimed in the patent, or whether it could have been derived (as alleged) by mutation of a micro-organism which, both sides agreed, was not of this species. In spite of the very considerable eminence of the patentee's witnesses, who concluded that the strain was *aureofaciens*, the British judge accepted the defendants' account of its origin. It is no exaggeration to state that problems of this kind, which are inherent in the typical biotechnology invention that involves deposition of highly valuable biological material, are unprecedented in the history of patent law.

Interested circles argued that the most logical time for making the deposited strain available was that at which publication occurs, upon or after the grant of the patent. A compromise alternative would be one in which the availability of the deposited strain at the early publication date could be restricted to an independent expert acting on behalf of a third party. The independent expert would be bound by all of the conditions attaching to original Rule 28 and he would therefore not be free to transmit the culture to the third party for whom he was acting. He could, nevertheless, perform all the experiments required on behalf of his principal to assess the sufficiency of the patent description and to enable the latter to form an opinion of the merit of the invention and its relevance to his own activities. This would meet the informational function of the patent disclosure and would enable competitors and others to prepare well in advance for the eventual filing of an Opposition to the granted patent.

The European Patent Organisation accepted the 'independent expert' proposal and introduced it into a new version of Rule 28. Provided that the applicant informs the Patent Office before preparations for publication of the application are completed, he may take advantage of the independent-expert option, according to which, in the interim between early publication and the eventual mention of the grant of the European patent, the deposited strain will be available only to an independent expert nominated by a third party from a list of experts recognized by the European Patent Office for these purposes.

In addition to the above amendment, the rule was modified by extending the scope of the undertakings made by persons obtaining a sample of the deposited organism. These now apply also to cultures 'derived' from the deposited culture, such being defined as those which are so derived and which still exhibit the characteristics of the deposited culture essential to carrying out the invention. This must include sub-cultures of the deposited strain and modifications thereof which meet the terms of the definition. Should any such modifications constitute or contribute to a further invention, however, their own deposition for the purposes of patent procedure is permitted.

Finally, an important amendment was made to the opening clause of the rule which specified the kind of micro-organism to which the rule is applicable. Originally this was simply defined as a micro-organism not already available to the public, but now there has been added the qualification 'and which cannot be described in the European patent application in such a manner as to enable the invention to be carried out by a person skilled in the art'. This amendment makes explicit the possibility of avoiding the need to deposit the new micro-organism where the applicant can justifiably rely on the reproducibility of a written description of the method of producing and identifying the micro-organism, e.g. by a repeatable technique of genetic manipulation.

The present situation on the release of deposited strains is summarized in *Figure 2*. UK, Germany and Switzerland are examples of countries which have maintained the original Rule 28 practice, whereas the current EPO practice, offering the independent-expert solution, has been adopted by France and Sweden and will be followed by others.

The current form of Rule 28 still falls short of being totally satisfactory to many applicants. The irrevocable nature of the deposit, even where no patent is obtained, is viewed as giving away a proprietary right in the biological material, independent of the patent right. Moreover, there is no restriction on the location of the independent expert who may obtain the culture. For microbiological inventions of the kind involved in the present discussion, the inventor who desires patent protection cannot avoid at some stage either making his new strain available to others or putting others in the position to reproduce the strain, i.e. to re-isolate or re-create it. The present drawbacks of depositing strains and accepting their consequential early availability to others have understandably given rise to discussion of the possibility of avoiding this requirement. In relation to recombinant strains and other organisms prepared by new biological techniques, it is being stated with

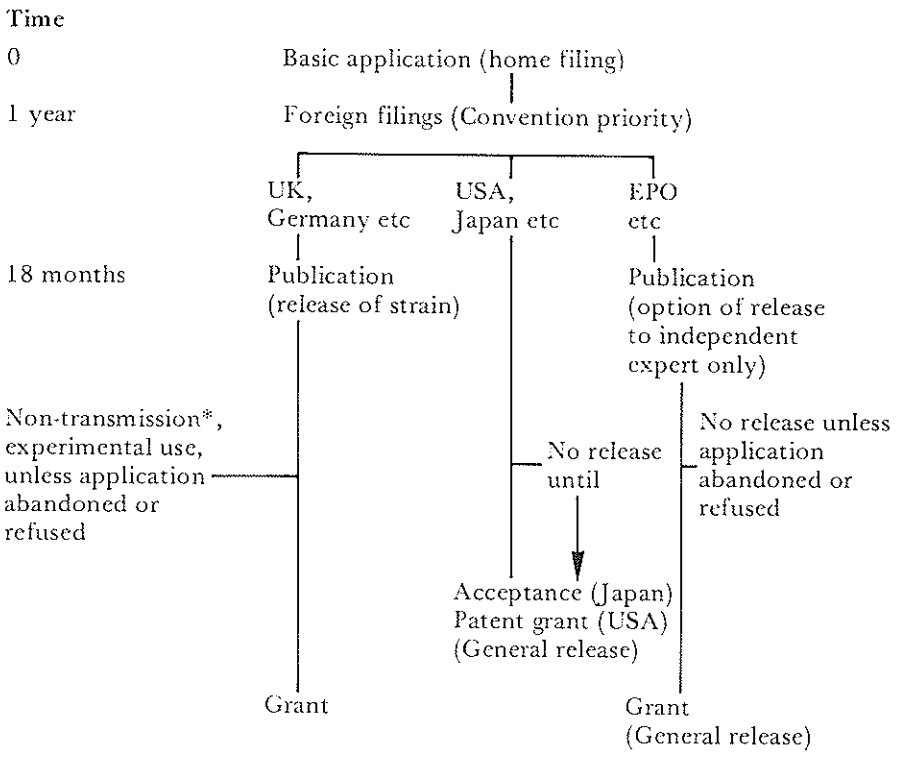

Figure 2. Release of deposited strains. **See* page 21 for conditions of release.

increasing confidence by some that the methods are becoming perfected to the stage at which they are reproducible from a written description alone. When such a consummation is achieved it will be a great relief to all who are involved in patents and the existing rules can be modified or reserved for the doubtful cases. The purist may say that the technique in different hands can never give rise to the identical new organism. However, absolute identity may not be fundamental for patent law. All that matters is that the invention claimed can be repeated but the law may not necessarily demand identical copies of what the inventor has achieved in his own laboratory. However, these are still uncharted waters.

Micro-organism patents

In both classical microbiology and the new biotechnology the following types of claim are encountered:

1. Process of producing a new micro-organism.

2. The new micro-organism as produced by the defined process.
3. The new micro-organism *per se*.
4. Process of cultivating or otherwise using a defined micro-organism to produce an end-product which may be:
   (a) a form of the multiplied micro-organism itself, for example vaccine or edible biomass;
   (b) a by-product of microbial growth, for example an antibiotic, enzyme, toxin, or an otherwise useful industrial product (even if inactive biologically); or
   (c) some other product or substrate which is produced or improved by the culturing process, for example a purified industrial product or effluent.
5. The products of any of the processes defined in (4)—defined by a *per se* claim or product-by-process claim as appropriate.
6. Particular formulations of new strains or cultures thereof, including combinations with other substances, designed to utilize and exploit their special properties, for example, in human or animal foods or for industrial uses.

Patents for process technology and specific applications of micro-organisms have been relatively uncontroversial as compared with those sought for the micro-organisms themselves. Thus for the Chakrabarty technology the process patent US 3,813,316 was granted within two years of its application date, whereas for the bacterium itself US patent 4,259,444 emerged only after a nine-year legal odyssey. This is another example of the occasional need for altruism by the few (in this case the General Electric Company) to take an expensive test case on an important point of principle.

The general excitement caused by the judgement of the United States Supreme Court (*Diamond* v. *Chakrabarty 1980*) in upholding the claim to a man-made organism has tended to overshadow the fact that the first high-level judicial decisions on the patentability of micro-organisms have come from Europe. In Germany, in keeping with the principles laid down in the Red Dove case described above, the Supreme Court has approved or denied *per se* claims in accordance with its ground rule of reproducibility. Again, following the chronological method, some of the main German decisions will be outlined.

In the *Baker's Yeast* case (1975) the applicants claimed two mutant strains of yeast by reference to their specific culture-collection accession numbers and a variety of process claims and use claims directed to the propagation of the defined strains by conventional methods and their use for pressed yeast or active dry yeast or for the production of baked goods. The Federal Supreme Court held that in order to obtain protection for a micro-organism *per se* (including one found in nature) the organism must be capable of being obtained by disclosure of a repeatable method of producing it without dependence on biological material provided by the applicant (such as by propagation from a sample deposited by the applicant). In the patent specification no method was disclosed for producing the mutants other than

through propagation of a culture of these same mutants. This was insufficient to meet the requirement of the prevailing patent law.

In the *7-chloro-6-demethyltetracyclin* case (1977), the invention was concerned with the production of mutant strains of *Streptomyces aureofaciens* which would selectively produce the title compound in preference to related tetracyclines, thereby obviating substantial purification problems. The micro-organism claims were directed to mutants of the type strain A-377 (NRRL 2209) characterized by selectivity for producing the desired compound and also by the colour of the fermentation mash expressed in terms of a numerically defined reflection curve. The latter parameter was a distinguishing mark by which strains having the desired properties could be recognized. In the appeal to the German Supreme Court, amended claims were presented which included culture-collection deposition numbers of exemplary mutant strains. However, these deposits had not been made until almost 3 years after the filing date of the application. Important though it was, the non-deposit of the strains at the proper date was not the central issue in this case. The primary ground of objection was that the mutants were obtained by treatment of the type strain with ultraviolet radiation or chemical mutagens, but no details of the process were given which would have been reproducible with reasonable certainty of success and with the expenditure of reasonable effort and cost. The characteristic colour of the fermentation mash was alleged to be a marker for recognizing suitable mutants once they had been produced. However, the random use of a mutagenic procedure followed by recognition of suitable mutants did not amount to a reproducible chain of steps which would be reasonably certain to produce the mutants. This lack of a reproducible process for the production of the mutants was fatal to the patentability of the mutant strains *per se*.

In the *Lactobacillus bavaricus* case (1978), however, the German Federal Patent Court upheld a claim to a group of naturally occurring micro-organisms to which the applicants gave the species name *Lactobacillus bavaricus*. The claim defined the micro-organisms as 'obtainable' by carrying out certain specified selection steps which resulted in the production of bacteria which predominantly produced the L(+) isomer of lactic acid. The claim was therefore to a new species of lactic acid bacteria characterized by a certain method of producing strains of this species but not limited to the use of such methods of production.

Although naturally occurring, the new micro-organisms had previously been undiscovered and required human technical intervention to recognize them and produce them in a reproducible manner. The subject matter of the application was therefore an invention and not a mere discovery. The court was persuaded that a reproducible description enabling the skilled person to produce (i.e. isolate) strains of this species had been given in the specification. The court also stated that the isolated pure cultures of the new species upon addition to the vegetable to be fermented (Sauerkraut) had a different effect compared with that achieved at naturally occurring concentrations in the vegetable source.

The insistence on the reproducibility issue is perhaps the reason why the German cases have not had as great an influence on the international

development of microbiological patent law as the Chakrabarty decision in the United States. Also, in Chakrabarty we are close to the new biotechnology, as the following main claim of the patent shows:

> A bacterium from the genus *Pseudomonas* containing therein at least two stable energy-generating plasmids, each of said plasmids providing a separate hydrocarbon degradative pathway.

The United States Patent and Trademark Office had maintained the argument that Congress had not intended living organisms to be encompassed by the terms 'manufacture' or 'composition of matter' under the US Patent Statute (35 USC 101). In addition they had argued that micro-organisms are products of nature and as such unpatentable. The first proposition was supported by the argument that the Plant Patent Act of 1930 and the Plant Variety Protection Act of 1970 showed the intention of Congress to limit the legal protection for living organisms to those specifically covered by these statutes and therefore to exclude bacteria from within the categories of patentable subject matter. In rejecting this argument the court held that Congress plainly contemplated that the patent laws would be given wide scope. The claim was not to a hitherto unknown natural phenomenon but to a non-naturally occurring manufacture or composition of matter, a product of human ingenuity having a distinctive known character and use. In also rejecting the 'product of nature' argument, the court held that the patentee had produced a new bacterium with markedly different characteristics from any found in nature and one having the potential for significant utility. This was not nature's handiwork but that of the inventor.

This decision has addressed the crucial question of novelty in patent law in the context of 'product of nature'. Had it been possible to show the fortuitous and even previously unknown occurrence in nature of a pseudomonad containing two or more different plasmids of the kind claimed, the decision would presumably have been otherwise. Fortunately, such was not the case and the decision stands as one of monumental importance to the future development of patent law in the USA and beyond.

Between the Baker's Yeast and Chakrabarty cases, negative decisions on the patentability of micro-organisms newly isolated from soil were given in Australia (1976) and Ireland (1978) in the *Rank Hovis McDougall* case.

The claims rejected by the Australian Commissioner of Patents were of the following type:

> *Fusarium graminearum* Schwabe deposited with the Commonwealth Mycological Institute and assigned the number IMI 14525 and variants and mutants thereof.

These novel strains had been developed as suitable for the production of edible protein. They were admittedly isolated from soil samples but no disclosure of the particular soil or particular method of isolation had been given. The specification was held insufficient because it did not describe any method of performance of the invention, i.e. it did not describe any method

of producing the micro-organisms. This requirement was not satisfied by mere deposition in a Culture Collection, even if a deposited strain was available by that means. The view was also taken that as the organism was isolated from a soil sample 'There may at best have been a discovery. No invention was involved in the mere discovery or the mere identification or the mere isolation by an unspecified method of something that occurs in nature.' In asking the rhetorical questions 'What has the inventor done, what contribution has he made?' the reply was 'He has discovered a naturally occurring micro-organism and by altering its conditions of growth he has changed its morphological characteristics. If that is all that he has done he has made no useful contribution to the art.' The decision indicated that the situation would be quite different if in producing the micro-organism by some man-controlled microbiological process the inventor were to have produced a new micro-organism having improved or altered useful properties. In the latter circumstances it would be wrong to refuse a patent for such an invention on the ground that such a micro-organism, being something living, was not a manner of manufacture.

The identical claim was also refused in the Irish High Court but for different reasons.

The Chakrabarty case is generally assessed as definitive in disposing of the objection that patents should be denied for micro-organisms simply because they are alive. In the *Abitibi Paper Corporation* case in Canada decided in 1982, the Commissioner of Patents was undoubtedly influenced by the attitude of the US Supreme Court and by other foreign case law. The Abitibi claim was to a combination of five micro-organisms acclimatized to spent sulphite liquor. Combination claims have not usually provoked the opposition reserved for claims in naked *per se* form to a single strain and the decision is therefore not remarkable on that ground as such. But, in allowing the claim, the decision discusses the subject as a whole and sees no reason why patents for life forms much higher than bacteria should be refused.

To the positive attitude now shown towards micro-organism patents in the major industrial countries mentioned so far, we must add the view of the European Patent Office explained in its official Guidelines, and the thorough analysis of the issue under European patent law given by an EPO officer writing in his personal capacity (Teschemacher, 1982). The European patent system has gone a fair way towards accommodating microbiological inventions although there is still room for greater perfection. As regards biological inventions more generally, the main surviving problem is one rooted in past objections to the patenting of *methods* of treatment and diagnosis carried out on the human or animal body. Method claims of this type would be used where the substances or apparatus involved are not themselves patentable. The explicit rejection of these claims applies both to humans and other animals where the method has a therapeutic as distinct from an economic purpose. The exclusion of such methods from patentability, which is based on lack of industrial applicability, has inevitably also passed into those national laws that have harmonized with the EPC. Attempts to evade this exclusion by presenting claims in the form of 'use of substance X in treatment of disease Y' have been supported by European writers (*see* especially White, 1984).

NATURALLY OCCURRING MICRO-ORGANISMS

Patent law postulates a division between pure science and the phenomena and creations of nature on the one hand and the applied or artificial contrivances devised for meeting human economic needs on the other. Thus the concept of 'discovery' is primarily intellectual in character, in contrast to that of 'invention' which has a practical utilitarian nature, and it has been recognized in patent law that some such distinction must be made in considering the kind of subject matter which is suitable for patent protection. For example, although the US patent statute does not explicitly treat discovery as different from invention, the distinction between them has always been present in case law. It is to be found again in the Chakrabarty case in the way the Supreme Court dealt with the argument that the handiworks of nature are above the patent law and free for all. The Court was able to reject the argument based on the unpatentability of natural phenomena by observing that the Chakrabarty micro-organism was a new bacterium which was non-naturally occurring. The patent law prevailing in Western Europe is typified by the European Patent Convention wherein 'discoveries' as such are one of the list of specific exclusions from patentability although the criteria for distinguishing between unpatentable discoveries and patentable inventions have been left open, presumably, for decision by case law.

For micro-organisms it seems appropriate at first sight to apply the term 'discovery' to organisms pre-existing as such in nature and the term 'invention' to non-naturally occurring organisms constructed by the new techniques of biotechnology, such as the recombinant DNA and hybridoma technologies. This line has the merit of being a clear and simple solution and it appears to be accepted by many commentators within the patent professional community and beyond.

An analysis of this issue must begin with the question of novelty. To take the European patent system as a model for discussion, the test for novelty is applied to the 'state of the art' which is defined as 'everything made available to the public by means of a written or oral description, by use, or in any other way, before the date of filing of the European patent application'. The same criterion is used when considering whether a micro-organism should be deposited in accordance with EPC Rule 28. A new micro-organism is one not already available to the public, e.g. not on open access in a Culture Collection or not so well known, so well identified and so ubiquitous in the environment that it may be recovered at will with minimal effort by the skilled worker. The necessary element of novelty, in the sense of previous inaccessibility, can be fulfilled in a variety of ways. A new micro-organism may be produced by purposive construction from a known and available organism by incorporating into it foreign genetic material. Alternatively, in the category now being discussed, a new strain may arise in the laboratory by chance mutation or some other fortuitous event. Yet again, a previously unknown micro-organism may be isolated for the first time from soil or other natural source.

At the extreme negative end of the spectrum of opinion, the isolation of 'found' micro-organisms is regarded as mere discovery and therefore unpatentable. The middle ground taken by most commentators is that the

technical teaching of an isolation procedure, or the mere fact of one having been required, adds the element of inventiveness necessary for patentability. Assuming also that some practical utility for the organism is demonstrated, two of the main criteria for patentability have thus been met. Inventiveness, the other criterion, flows almost automatically from the combination of novelty and utility, assuming of course that it was not obvious (1) that the specific organism existed, (2) how to isolate it and (3) that it would have the useful properties shown for it. The adherents of this position usually suggest that the claim to the micro-organism must not directly cover the organism in its natural state and some kind of purity limitation is called for as, for example, in USA where the claim must recite a 'biologically pure' culture. The most positive approach to patents in this situation regards the purity limitation as contrived and really unnecessary. For what did it profit the skilled worker that the micro-organism existed in nature, if that existence was previously unrecognized and therefore unutilized? In those circumstances it could not be a part of the state of the art as commonly understood in relation to what is previously known from documents or used in the technology. In practice, such a restricted claim may give sufficient protection in most cases, but one can conceive circumstances in which the purity limitation may be inconvenient and impose a difficult burden of proof on the patentee.

The arguments outlined here are relevant to the natural-product problem as a whole and not only to micro-organisms. An important recent contribution to the debate is the decision of the Federal Patent Court in Germany on the *Antamanide* case. The claim was to a cyclic decapeptide termed antamanide, which was a naturally occurring substance present in the green amanite fungus. Here, the Federal Patent Court addressed itself to the problem of differentiating between discovery and invention. The court was convinced that this was not a case of mere discovery because, although the inventor had discovered the existence of this valuable peptide in nature, he had not restricted himself to a non-patentable discovery but had gone further and provided a technical teaching of the process of preparing the substance. The fact that the substance existed in nature was not *per se* a circumstance detracting from novelty, provided that the average expert was not previously aware of the fact. The court therefore approached the legal problem on the basis not of pre-existence but of availability or otherwise to the public, i.e. it applied a strict state-of-the-art test. A naturally occurring substance which *was* previously available to the public would be no longer novel in the patent law sense, but that was not the situation here. As to whether there was any difference of identity between the claimed compound and the decapeptide in the form in which it existed in nature (a question of fact which was not resolved), the court took the liberal view that this would not in any event be decisive as regards the allowability of a claim in the *per se* form used.

The significance of this case is that it is modern and decided under national law in conformity with the principles laid down in the guidelines of the European Patent Office. Most other 'product of nature' cases are now relatively old and were decided under United States jurisprudence. This case is therefore helpful on the whole question of 'products of nature' under

modern patent law and is significant not only for genetic engineering and the vectors and other immediates used therein but also for inventions in a wider research area involving the isolation of valuable substances from natural sources.

PATENTS FOR GENETIC MANIPULATION

The Cohen-Boyer US Patent 4,237,224 was the first patent granted in the United States for recombinant DNA techniques, but others had appeared relatively unnoticed and unsung in other countries. The grant of the Cohen-Boyer patent opened the log-jam in the US Patent Office and many patents in this field have since issued. The present period is one in which both the combined creativity of inventor and patent draftsman and the official response to it will determine the kinds of patent that can emerge from prosecution and examination in Patent Office proceedings. Claims to synthetic genes and plasmids in terms of functional properties and specific restriction maps, as well as those drafted more concretely in terms of DNA sequences, are all appearing, together with claims to recombinant strains and other scientific creations. The categories of patent in this field have been postulated by some authors (Vossius, 1979; Hüni and Buss, 1982) and many specific examples have been quoted in an early overview of this developing field (Halluin, 1982). A highly perceptive analysis of the legal issues involved in various types of claim to newly isolated or newly constructed plasmids and other DNA combinations has been given in an academic study (Bendt, 1982). A summary of a review of published patent applications and patents in genetic engineering up to 1982 and beyond (Knuth *et al.*, 1984) indicates that a wide variety of terminology has been used by applicants for the characterization of the molecules and other entities involved, and these latter authors suggest the need for more uniformity of definition in this field.

There is clearly inspiration in the writing of genetic engineering patents as well as in the inventing of what goes into them, and the observer can only marvel at the ingenuity of the pacemakers. It will be the case law which finally brings discipline into the draftsman's art and so far the signposts are few. The greatest interest will focus around the level of inventiveness required to sustain claims of the broad scope that are required to block effectively the loopholes through which competitors can slip with their own specific sequences and clones. Inventiveness is the acid test of any patent. Its resolution is an enormous problem for legal systems in which judges with specific technical knowledge are the exception and not the rule. The claiming of vectors and other DNA molecules in broad and purely functional terms, i.e. reciting the end result intended to be produced by the components of the system (control region, structural gene sequences, etc) is in danger of being held unacceptable as a mere statement of a problem or an obvious desideratum even though supported by one or more of the characteristic Examples to be found in patent specifications.

The classic conception of invention is the finding of something unexpected or the doing of something unusual, proceeding perhaps down a path away

from the normal direction of research. This is not easily equated with the demonstration of great scientific skill as such. It is likely in this field, however, that arguments for inventiveness may place more reliance in future on the degree of expertise displayed in overcoming problems of scientific experimentation than has been done in the past in less complex technologies.

Some of the recombinant-DNA patents that have issued may soon be tested as the parties begin to shape up for disputes over priority and scope of patent claims. In view of the complexity of the issues involved, this writer has no intention of predicting the case law before any of it happens. As these new general techniques yield their fruits when applied to the production of particular biologically useful peptides and proteins by the efficient methods of the fermentation industry, the inventiveness of specific applications will inevitably be called into question. Much will depend on the scope of what is claimed as new and as more than the obvious application of a new tool to fashion specific end-products.

On the question of inventiveness and claim scope, one case which is particularly noteworthy has been decided at Patent Office level. This involved the application of cell-fusion techniques to the construction of hybridomas for the production of monoclonal antibodies. After the discovery of the basic technique and the subsequent appreciation of its 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 much the same way as should apply to the patenting of particular applications of recombinant DNA methodology. Mere novelty should not be enough. This approach has been vindicated in the *Wistar Institute* case in which claims so broadly drafted as to cover the application of the basic method to the preparation of viral antibodies could not be sustained. Rejection of an attempt to re-patent the basic technique as applied to such a broad sub-class of antibodies is less noteworthy, however, than the rejection even of the specific claim to an individual hybridoma on the grounds of lack of any stated exceptional quality which would justify patent protection.

Patents for plants and other organisms

There is now a clear trend in favour of allowing patents for organisms of the kind with which the industrial microbiologist is principally concerned. These are now widely seen to be tools as useful to industry as are chemical compounds. An extension of this thinking to certain higher organisms has already been achieved without perceptible difficulty. Thus, animal and other cell cultures and cell lines have not so far been distinguished from bacteria and other simple organisms in the consideration of patentability by patent-examining authorities. Cell lines, for example, are treated as micro-organisms for the purpose of existing legislation and are regularly deposited in Culture Collections for patent purposes. At some stage in the scale of life forms, however, an obstacle is reached either by statute or by a prevailing ethos against granting patents for higher organisms of a certain size and complexity.

The most explicit legal restriction on patents for plants and animals is to be found in Article 53(b) of the European Patent Convention, as follows:

> European patents shall not be granted in respect of:
> (a) . . .
> (b) 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.

THE LEGAL PROTECTION OF NEW PLANTS

Legal systems for the protection of new types of plant are of relatively recent origin compared with patent laws. This is attributable in part to the fact that scientific plant breeding did not begin until the laws of genetic inheritance were recognized in the early part of the present century. In addition, it was commonly considered that the difficulty of transferring plant-breeding technology reproducibly by means of the written description must remove it from the ambit of the patent law. A further reason may be found in the lack of sufficient pressure from the industry to provide legal forms of protection, until more recently. Indeed, trade secrecy is still regarded by some as a more effective method of achieving protection: for certain hybrid plants, for example, the ability to retain exclusive possession of the parental lines may give the breeder all the protection he needs.

In contemplating possible systems of protection, one must consider the whole plant, the reproductive material of the plant, and the flowers or fruit or other consumption material produced by the plant. The traditional patent system has hitherto been viewed in most countries as inappropriate for the protection of new types and varieties of plant, but a small minority has provided for plant patents. The most well-known is the special type of plant patent granted in the United States under the Plant Patent Act of 1930 which is now incorporated into the general statute of patents. This type of patent is available for asexually reproducing plants and covers the whole plant; most plant patents are taken out for rose trees and fruit trees. The other well-known system is that in Germany where patents for plants began to be granted under the ordinary patent law in the 1930s.

Plant variety rights

The plant variety right is a special type of protection which was introduced into many national laws in the 1960s and was also made the subject of the International Convention for the Protection of new Varieties of Plants (UPOV) which was signed in 1961 and became effective from 1968 onwards.

Whereas with plant patents of the United States type the protection is for the whole plant, it is a general characteristic of plant variety protection that it is directed to the reproductive material of the plant. The plant variety right covers the production of the reproductive or vegetative propagating material

for the purposes of commercial marketing, its offer for sale, and its marketing. This form of right is adapted so much to the special circumstances of the plant breeding and growing industry that its procurement and exploitation is a highly specialized business. The establishment of the plant variety right system has been followed by substantial private industrial and public investment in plant breeding with the resulting development and introduction into agriculture and horticulture of many new varieties of plant. Nevertheless, the limited scope of the right has been the subject of critical comment in recent years. The UPOV Convention prohibits the possibility of double protection, i.e. by both patent and plant variety right (Straus, 1984). The plant variety right is adapted to the traditional operations of the plant breeder, from which there finally emerges a variety which has the desired combination of traits and is stable and homogeneous. This kind of activity, although it clearly involves intervention by the skilled worker in the natural process, is not seen as technical intervention of the kind which patent authorities will recognize as coming within their domain. It is a long-drawn-out process incapable of realistic commitment to writing with a view to reproducibility, a factor which gave rise to frequent difficulty in the protection of plants under the German patent law. The development of new varieties by these techniques and the prescribed test procedures typically required for plant variety protection and for official certification of the new variety for industrial use are outside the remit of patent-examining authorities. For this reason it is understandable that legislators of the patent law have insisted on a separation between the two systems.

Plant genetic manipulation poses a new situation. It clearly involves technical intervention of the kind which may be capable of reproducible written description along similar lines to that used for recombinant-DNA inventions. It is therefore appropriate to question whether the processes and products of plant genetic manipulation should be assumed to come automatically under the present ban in EPC and similar patent law. A technique which can be described in a reproducible manner and which leads to genetically altered plants could be viewed as an *invention* within the scope of the patent law, protectable as a process and also by means of product *per se* claims to new plants defined by appropriate characteristics. If genetic manipulation is a 'microbiological process' it follows that its products are patentable, regardless of whether they are plants or animals. Furthermore, by limiting the term 'plant variety' to those specific entities which in context are clearly subject matter most appropriate for protection by means of a plant variety right, it would then be possible to allow patent protection for subject matter which is more correctly categorized as 'invention', even though the type of protection sought involved the presentation of claims to plants as such. These claims could be regarded as not directed to a 'plant variety' but rather to an inventive concept relevant to a much wider grouping or definition of plant materials than is connoted by the term 'variety'. Such an approach is already possible, for example, under United States law where the ordinary (utility) patent is available for inventions which are amenable to the verbally formulated patent claim and the corresponding enabling disclosure in written form.

The question of copyright

It has been suggested that the law of copyright may apply to the works of 'authorship' of the genetic manipulator (Kayton, 1982). Opinion is divided on this question among the few US authors who have so far commented on it (*see* for example Cooper, 1982b). To most patent experts the notion of copyright for, say, a recombinant plasmid seems bizarre even in spite of the intriguing analogy with a computer program. As an academic legal possibility the question is of interest, but as a practical reality it may evaporate as soon as the problem of actual enforcement of copyright comes to be considered. Copyright vests not in a fundamental idea but in a mode of expression of that idea and it is therefore essentially a narrow form of legal protection. In addition, if it is to be enforced, there must have been actual copying of the original work and not independent invention. In the light of the specific patent disputes that are now in prospect, it is difficult to envisage copyright as having any conceivable application to such situations.

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