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Managing genetic material to protect intellectual property rights

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One of the most important policy instruments for the promotion of further biotechnology development is intellectual property right (IPR) protection. However, one cannot improve upon a biotechnological invention without physical access to the germplasm, making exchanges of genetic material necessary. A formal transfer agreement, which addresses the key issues of ownership, access, use, and equitable benefit-sharing, is a powerful legal instrument for intellectual property. Other restrictions are generally imposed as a result of national and international safety regulations. Forming strategic alliances, such as joint ventures, collaborative research agreements, joint research and development agreements, and manufacturing and distribution alliances to exploit the economic value of genetic material, provides scientists with the mechanisms they need to bring their research material and products to the marketplace.

Keywords: genetic resources; biotechnology; intellectual property right (IPR) protection; patent law; material transfer agreement

Introduction

Genetic resources include recombinant DNA, plasmids, gene constructs, chimeras, probes, microorganisms, animals, plants, and all associated information. Genetic material was once in the public domain and accessible to the entire scientific community, but in the last few decades major changes have taken place. Advances in biotechnology and molecular genetics now provide powerful tools for the isolation and characterization of valuable traits with enormous economic potential. Techniques have been devised for transferring genetic material between completely dissimilar organisms and for using living organisms to produce chemicals, drugs, and metabolic products.

Thus, the use or application of that same material may now be judged an intellectual property right (IPR) with legal protection granted by sovereign authority. IPRs allow right holders to enhance the genetic material being used and technology being developed, prevent others from patenting the invention, recoup investments, establish market position, preserve the identity, and generate revenues through forming strategic alliances, such as joint ventures, collaborative research agreements, joint research and development agreements, manufacturing and distribution alliances, and cross-licensing arrangements.

One of the most important policy instruments for the promotion of further biotechnology development is IPR protection to safeguard economic interests. Starting in the 1980s, the large industrialized countries began international negotions to encourage the rest of the world to reduce unauthorized distribution of genetic materials and new technologies. A number of bilateral and multilateral initiatives have been taken or are being implemented to harmonize IPR protection worldwide. Harmonization for most, if not all, countries will mean introducing much stricter IPR protection that can have far-reaching consequences for discovery of, access to, and use of genetic material and knowledge.

Some countries, led by the United States, have initiated bilateral negotiations to secure stronger protection for the intellectual property of their nationals. The United States has granted favored-trading status only to those nations that meet rigid IPR protection standards. European countries have done the same. On the other hand, the absence of strong IPR protection acts as an effective trade barrier [6].

Ownership/sovereign rights to genetic material

The first international agreement to recognize countries' sovereign rights with respect to genetic resources was the 1983 United Nations Food and Agriculture Organization (FAO) International Undertaking on Plant Genetic Resources. It adopted the premise that freely accessible genetic materials are the common heritage of humankind to be conserved and used for the benefit of all. In 1989 a modification of the Undertaking clarified that free access to those materials no longer meant free of charge. A 1991 FAO conference endorsed nations having sovereign rights over their genetic resources, including breeders' lines and

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Abbreviations used: APHIS, Animal and Plant Health Inspection Service; CBD, Convention on Biological Diversity; CDC, Centers for Disease Control (and Prevention); CLIA, Clinical Laboratory Improvement Amendment; DMM, Domestic Mail Manual; DOC, (United States) Department of Commerce; DOT, (United States) Department of Transportation; EC, European Community; ECCN, Export Control Classification Number; EPC, European Patent Convention; FAO, (United Nations) Food and Agriculture Organization; GATT, General Agreement on Tariffs and Trade; GMO, genetically modified organism; IATA, International Air Transport Association; ICAO, International Civil Aviation Organization; IDA, International Depository Authority; IMM, International Mail Manual; IMO, International Maritime Organization; IPR, intellectual property right; MAA, material acquisition agreement; MTA, material transfer agreement; PCT, Paris Convention Treaty; PPQ, Protection and Quarantine Program; TRIPS, Trade Related Aspects of Intellectual Property Rights; USDA, United States Department of Agriculture; USPHS, United States Public Health Service; USPS, United States Postal Service; USPTO, United States Patent and Trademark Office; WIPO, World Intellectual Property Organization; WTO, World Trade Organization

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farmers' breeding material, which are made available at the discretion of their developers during the period of development [11].

Effects of GATT on patent laws

Under the General Agreement on Tariffs and Trade (GATT) bilateral actions were extended to multilateral negotiation of trade-related intellectual property issues. Protection of biological innovations was introduced in the GATT talks in 1990 and became the subject of specific provisions in the final agreement. To become a member of the World Trade Organization (WTO), according to the Uruguay Round of GATT, a country must adopt the agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) which requires that patents be available for any invention in all fields of technology. TRIPS is the most comprehensive international mechanism ever negotiated on IPR. Its provisions constitute minimum standards for the protection of IPRs for biotechnological inventions.

Several articles in the TRIPS agreement deal with patentability. According to article 27.3, parties may exclude from patentability: (1) plants and animals, other than microorganisms; and (2) essentially biological processes for the production of plants or animals, other than non-biological and microbiological processes. This article will be reviewed 4 years after the entry into force of the WTO agreement, indicating the difficulties inherent to biotechnological issues. Two other provisions in the TRIPS agreement include: (1) protection of a process is extended to the products directly made with said process (article 28.1.b); and (2) in civil proceedings related to process patents, the reversal of the burden of proof is established (article 34) [12].

In most developing countries, lack of a competitive market, limited research facilities, and lack of participation of industrial sectors in innovative activities represent serious obstacles to capitalize on the benefits of a modern system of IPR protection. Despite the progress made by many developing countries to adapt their regulations to TRIPS, it still will be difficult to enforce them. Most countries lack the institutions and personnel for safeguarding IPR. It is also unclear to what extent developing countries, where a significant part of biodiversity is found, will be able to profit from sovereign rights envisioned in the Convention on Biological Diversity (CBD).

Convention on Biological Diversity (CBD)

In 1993 the CBD became a legally binding framework for conserving and utilizing global biological diversity. It recognizes national sovereign rights over all genetic resources, as well as the need to compensate developing countries for the resources they have provided to the industrialized world. The CBD grants access to those resources in exchange for compensation and technology transfer. Authority to determine access to genetic resources rests within the national governments and is subject to national legislation. Access is subject to prior informed consent and based on mutally agreed terms. The CBD provides for the sharing of benefits from genetic resources with the country of origin. This implies that future transfers of genetic resources will be made under material acquisition agreements (MAAs) and material transfer agreements (MTAs) designed to protect source nations' interests in any resulting profits [5].

The CBD guarantees protection of IPR under existing international laws and does not intend to restrict the availability of genetic resources. However, the Convention does reject the free flow of resources, that is, the 'common heritage' concept. This implies that any future collector of genetic materials will have to sign the equivalent of a MTA, and presumably agree to track the uses of the material, and to ensure that the donor nation receives a share of any profits that may be realized from the material. By terms of the Convention the national sovereign right concept applies only to material collected in the future and not to material already housed in culture collections. There are proposals for efforts to define source nation rights over those materials already conserved [2,3].

Patenting in biotechnology

Germplasm protection is a form of recognition and reward for conducting quality research and product and process development [1]. For a biotechnological invention involving genetic material to receive a patent, it must be 'useful', 'novel,' and 'non-obvious' to one of ordinary skill in that art. The utility requirement can generally be met by demonstrating a particular use, such as an isolated and purified DNA that can be used to make a therapeutic protein or act as an intermediate in the manufacture of an encoded protein with an established function. An invention is considered novel if it has not been placed in the public domain, that is, not described in a publication or available in commerce. A non-obvious invention is one that could not have been made with a reasonable expectation of success by a person of 'ordinary skill' in the relevant scientific field from publicly available information.

It should be emphasized that the patent system applies to technology, not science. 'Useful arts' is an outdated term for technology, the downstream useful product of science. Thus, the original donor of cells used to develop a cell line cannot claim to be an inventor under patent law, since he or she usually has no conception of the potential of those cells and will play no technical part in the development of a useful product.

Every patent is an exposition of a problem, the solution to the problem, and the many opportunities seen by the inventor for elaboration and practical use of his findings. Physically, a patent includes a printed specification and one or more appended patent claims. The specification contains a written description that describes to a person of ordinary skill in the art how to practice the invention over the full length and breadth of the claims. Patentability depends not only on the breadth of the individual claims but also on the disclosure of what the inventor regards as the best way of practicing the invention. Full disclosure of an invention includes: (1) a written description; (2) enablement; and (3) the best mode known to the inventor at the time of the invention [9].

Certain elements are included in a patent application, usually in the following order:

(1) A statement of the field of technology, that is, the subject.
(2) A discussion of the prior art, that is, background information, and a statement of the problem to be solved.
(3) Statements of the 'objects' of the invention, that is, the benefits provided by the inventor's discovery.
(4) A summary or 'definition' of the invention, that is, the solution to the problem that the invention provides, stated in technical terms.
(5) Detailed elaboration of all aspects of the invention as summarized in the definition.
(6) A description of the usefulness or 'utility' of the invention.
(7) Working examples.
(8) Claims, the legal description of what has been granted as an exclusive right to the inventor.

The claims are the heart of a patent and must be read in light of the specification. They are the legal description of the grant of rights to the composition, process, or product that the owner may exclude others from using for the life of the patent. If an inventor claims less than what is disclosed in the specifications, he will only gain the scope of what is in the claims. The focus of patentability and infringement analysis is therefore on the particular claims and claim formats that are used to describe the limits of patent protection. Patent property differs from real property in the sense that others can obtain claims to improvements on the broad claim.

Living organisms and their products have increasingly become involved in modern technology [7]. In fact, biotechnology is defined as the application of living material to obtain useful products or services. It is now well established that biotechnological subject matter is patentable, and the focus is the scope of the claims. In the United States not only new products and processes that involve biological material, but also the biological material itself, if it is the result of an invention, may receive patent protection. Therefore, for an invention involving biological material, both the prosecution history, which is the 'undisputed public record' of proceedings in the patent office, and the biological material, which is deposited in the culture collection, are of primary significance in understanding the claims.

Deposit requirements

The requirement that the technology behind the claimed invention be reproducible and available to the public is the basic *quid pro quo* (equally reciprocal exchange) of the patent system. Because of the complexity of living systems and the difficulty of repeating certain experiments, words alone, or even words coupled with a reasonable amount of experimentation, may be inadequate to reproduce a biotechnological invention. Under patent practice, an applicant may deposit a sample of the relevant living material to supplement the description in the patent specification [8]. The description and deposit together constitute an enabling disclosure. For example, a claim to a fermentation method using a specific yeast strain might well require the deposit of the living material even though it is neither claimed nor separately patentable. Therefore, a deposit of the living material in a public depository is not only allowed, but mandated by patent offices to provide reference material. More importantly, a deposit enables samples to be made available to the public. Access to the deposited material is regulated by the particular patent system under which the application was filed. As part of the patent specification, patent deposits can be used in providing evidence or proof of patent invalidity or infringement after the relevant patent is granted.

The current regulations under which the United States Patent and Trademark Office (USPTO) will accept a deposit to satisfy full disclosure are found in the *US Federal Register* of August 22, 1989, and became effective January 1, 1990 (37 CFR 1.801–1.809). These rules are not primarily concerned with the substantive issue of whether a deposit is needed, although they state that the issue typically arises under the enablement requirement. Instead, they set forth the examining procedures and conditions that must be satisfied in the event a deposit is required by the patent examiner. The rules emphasize the need for the permanency of the deposit during the life of the patent and of its availability to persons having access to the pending application and to the public without restriction after the patent issues. The current United States deposit regulations do not require that a deposit be made prior to the filing date of the application. However, in many foreign countries the deposit must be made before the filing date of the priority application in order to obtain foreign priority rights under the Paris Convention Treaty (PCT). This consideration makes a prefiling deposit virtually mandatory in many biotechnology applications.

The European Patent Convention (EPC) provided for the deposit of a new microorganism in its original Rule 28 but did not restrict its availability during the time between the publication of the application and the granting of the European patent. In June 1980 Rule 28 was amended so that during this period the strain is available only to an independent expert at the discretion of the inventor and not to third parties. Details concerning the need for deposit, timing of deposit, release of deposit, jurisdiction of third parties, and availability during the patenting process vary from country to country.

The Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure drafted by the World Intellectual Property Organization (WIPO) eliminates the need for multiple deposits when patent protection for inventions is sought in more than one country. Under the Budapest Treaty, which came into force in 1980, a single deposit of a microorganism with a recognized depository (an International Depository Authority or IDA approved by WIPO) satisfies the requirement of all the countries under the PCT or the EPC. Such a deposit is also recognized by the USPTO. The Treaty requires that the deposit be tested for viability. The term of the deposit is 30 years from the date of deposit and at least 5 years after the most recent request for a sample. It does not address the timing of deposit or release, which are determined by the relevant national laws. For purely national purposes, deposit under the Treaty is often not

necessary. However, it provides the best system for the international recognition of a single deposit [8,9].

Regulatory compliance on acquisition and distribution of materials

Restrictions on the handling, storage, distribution, importing and exporting of genetic materials are generally imposed as a result of national and international safety regulations. Existing regulations primarily relate to hazards to human health and the environment, the transport of materials, and quarantine laws [10].

Because some biological material is pathogenic or of a hazardous nature, regulations for packaging and shipping are well defined by several United States federal agencies, including the US Public Health Service (USPHS), the US Department of Agriculture (USDA), and the US Department of Transportation (DOT). International shipments are also governed by the rules and regulations of the US Department of Treasury (Customs Service) and the US Department of Commerce (DOC).

Plant pathogens are organisms which can directly or indirectly injure, or cause disease, or damage in any plant or plant part, or any processed, manufactured, or other products of plants. The USDA regulates the movement of all plant pathogens across interstate or international boundaries and requires a permit from the Plant Protection and Quarantine Program (PPQ) for doing so (7 CFR Part 330). An organism that has been genetically engineered via recombinant DNA techniques from a donor organism, vector, or vector agent that is a plant pest or contains plant pest components requires APHIS Form 2000 (7 CFR Part 340).

The Animal and Plant Health Inspection Service (APHIS) of the USDA requires Form VS 16-3 for the importation of pathogens of livestock or poultry that are extremely virulent or for which there is a national eradication control program.

The USPHS requires a permit (CDC 0.753) for importation of any viable organism or its toxin that causes, or may cause, human disease. The regulation is administered by the Centers for Disease Control and Prevention (CDC) through its Foreign Quarantine Program. The CDC also regulates the packaging and shipping of human pathogens for interstate transport (42 CFR 72.3).

After recent terrorist incidents, stricter controls on the possession, transfer, and use of biological agents were developed to ensure protection of public safety without encumbering legitimate scientific and medical research. A final ruling was published in the *Federal Register* October 24, 1996. It (1) includes a list of infectious agents and toxins ('select agents') that are regarded as possible agents of interest to terrorists and establishes a process for changing that list when new information becomes available; (2) establishes a system of safeguards to be followed when these agents are transported; (3) establishes a system for tracking the acquisition and transfer of select agents between laboratories; and (4) establishes a process for alerting appropriate law enforcement authorities if an unauthorized attempt is made to acquire one of these agents.

Public and private laboratories, commercial companies, academic and research institutions, and other facilities that wish to transfer or receive the select agents will be required to register their facilities with CDC. Facilities will be subject to inspection to verify the information provided at the time of registration. Only registered facilities will be able to transfer or receive select agents, and documentation of each transfer will be required. Clinical laboratories certified under the Clinical Laboratory Improvement Amendment (CLIA) of 1988 that intend to use and transfer select agents only for diagnostic, reference, verification, or proficiency-testing purposes are exempt from the requirements of the regulation.

The DOC regulates the export of biological material through the Bureau of Export Administration. Any organism or toxin that appears under Export Control Classification Number (ECCN) 1C61B requires a validated export license for all foreign destinations except Canada. The DOC was recently requested by Congress to identify organisms that might be involved in biological warfare and to place export controls on them. A new ruling, effective August 8, 1996, minimally increases the number of validated export licenses required for certain viruses, rickettsiae, bacteria, fungi, certain toxins or subunits, and genetically modified organisms or genetic elements that contain nucleic acid sequences associated with pathogenicity and are derived from organisms, plant pathogens, or toxins on the list. Immunotoxins, which are therapeutics with no biological warfare application, are now excluded.

The transport of biological material between countries is regulated by the International Postal Union, the International Civil Aviation Organization (ICAO), and the International Maritime Organization (IMO). Recommendations drafted by the United Nations Committee on Transport of Dangerous Goods are enforced by ICAO and IMO. The International Air Transport Association (IATA), a trade organization of airlines, publishes a manual of air transport procedures in agreement with the ICAO regulations, which are accepted by freight carriers worldwide. Because most material is sent by air, IATA regulations must be followed whether the flight is by Postal Service or freight carrier.

There has been some attempt at harmonization between the United States federal agencies and their European counterparts. For example, the DOT has accepted the UN and IATA requirements for transportation of hazardous materials and the Food and Drug Administration is working with the European Community (EC).

Hazardous cultures must be packaged to contain all contents in the event of damage to the package or breakage of vials. Proper packaging includes placing the primary container (culture vessel) into a leak-proof secondary container with sufficient absorbent material to contain all liquid in the event of breakage. The package must be marked appropriately with the required labels.

In the United States biological material may be shipped by the Postal Service or private freight carrier. Shippers are responsible for the safety of those handling and receiving the material. The US Postal Service (USPS) in the Domestic Mail Manual (DMM) and International Mail Manual (IMM) and the DOT in 49 CFR Part 173 all require that etiological agents be packaged in accordance with the USPHS guidelines in 42 CFR Part 72. The DOT describes

requirements for packages containing infectious substances in 49 CFR Part 178.609.

Ever since its introduction in the 1970s, the regulation of rDNA technology has been a matter of concern. However, time has shown that the initially perceived hazards of gene cloning and its potential adverse effects on the environment appear to be unfounded. To date the most successful approach in regulation has been based on the fact that biosafety guidelines developed for the containment of pathogens are effective regardless of whether or not the pathogen is a genetically modified organism (GMO). Once a risk assessment is made, appropriate containment levels can be prescribed.

Material transfer agreements

Living organisms are difficult to describe verbally and impossible to duplicate from a written patent description. Thus, the availability of living material is more important in a biotechnology patent than in any other type of intellectual property. One cannot improve upon a biotechnology invention without physical access to the germplasm, making exchanges of genetic material essential for advancement of science and technology.

Agreements to transfer material can range from a very formal written document to an informal exchange with no exceptions or implied limitations on use of the materials. A 'free exchange' is understood to mean an exchange of an unrestricted nature, that is, available to anyone, while 'exchange for free' means that there are no costs involved [4].

A material transfer agreement is a powerful legal instrument for intellectual property. It has the advantage of binding the parties involved and their successors to an agreement before a patent issues, after it expires, and even if it never issues. Most often it is the lack of this type of agreement that results in litigation. Even a simple transfer agreement can provide important legal rights. Without it, certain statutory and implied obligations may or may not be imposed by a court. Therefore, it makes sense to reach at least a basic agreement before transferring samples of biological material to another researcher, especially if the research has any commercial potential.

All genetic material has the potential to contain protectable intellectual property and any limitations on ownership or commercialization opportunities must be made clear by the owner. It is important that the following key issues and questions be addressed in negotiating a material transfer agreement.

Ownership

- Are there clearly defined ownership/sovereign rights to the genetic material, either as intellectual or personal property?
- Does the contributor have full ownership rights and ability to transfer?
- Does the contributor have full title to the material and all its parts and products?
- What is the status of any applications for intellectual property rights?
- Are there any existing agreements or understandings, written or verbal, involving the material?
- Was the material developed through funding by a government agency in whole or in part?

Access restrictions

- Are fees or compensations, if any, for transfer of the material defined?
- Is distribution of substances and/or derivatives created from the transferred material, not within the definition of original material transferred, permitted?
- Is transfer to third parties limited?
- What is the current system for making the material available, ie, what is the nature of the industry for the material?
- What is the amount of material available, how is it generated, how would it be made available for commercialization?
- Are there points in the industry or the distribution system which can be readily accessed or utilized to manage or control the material?
- Does the inventor need to or want to have a role in supplying the material?
- Is the material transferred to be returned or destroyed upon termination of the transaction?

Use restrictions

- Is the contributor granting exclusive rights or nonexclusive rights?
- Have any warranties or representations been made by the contributor?
- What is the scope of use permitted, ie, use for research purposes only?
- Are any territorial restrictions or field of use restrictions in existence or sanctioned by sovereign authority?
- Are any applicable government statutes, regulations and voluntary guidelines, or product liability insurance required for utilization?
- Are any potential tax implications or potential antitrust problems subject to the jurisdiction of sovereign authority?
- Are there existing standards or accepted norms for this type of material?
- Are there existing public/private sector relationships pertinent to this material?
- Does the user have an existing licensing obligation to a third party?

Benefit-sharing

- What is the commercial status of the material, ie, does it need further development, or is it ready to be marketed or used?
- What is the economics of the material? Is it of primary value or a downstream product?
- What capability is required to bring the material to the marketplace?
- Is there other material that is critical or contributes to the successful use of the material?

- Do the transferred rights involve any intellectual property rights owned by the contributor?
- Who has the rights to any patent, if a patentable invention results from the material? Will the contributor or the user file, prosecute, and maintain the patent?
- What is the potential commercial life expectancy of the material?
- Is an option available to license commercially useful embodiments or improvements produced by the user of the material?

Future perspectives

The new international framework for the protection of biotechnologies under IPR has satisfied those who had pressured for change. It is widely accepted that an invention consisting of or using living matter should be protected by IPR. In a situation where strong IPR protection has been established, foreign biotechnology companies can be expected to be more interested in exporting their genetic material and technologies derived from this material to a country with such protection. Lack of IPR protection will bar trade.

With the availability of IPR protection of biotechnologies and prospects of vast markets for biotechnological products and techniques in industrialized countries, the bulk of the necessary research is funded, carried out, and controlled by the private sector. The new framework for the protection of biotechnologies under IPR can also be expected to produce an increase in private research activity. In the United States, Europe, and Japan, it is estimated that about 60 percent of the funding for biotechnology R&D comes from the private sector. IPR protection can also facilitate the rapid availability of genetic material and associated technology via licensing agreements and other contractual agreements. Protection of IPR plays an important role in creating a safe climate for material transfer. It should be integrated into a strategy that should involve closer relationships between science, technology and the market. The global germplasm system in the future may be evaluated by how quickly developing countries agree to establish an effective system to protect intellectual property of biotechnology inventions. More and more laboratories, institutions, and companies are forming strategic alliances, such as collaborative research agreements, joint research and development agreements, joint ventures, and manufacturing and distribution alliances, to exploit the economic value of genetic material, thus providing scientists with the tools they need to bring their research material and products to the marketplace.

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