Journal of Food and Drug Analysis
1996. 4(3) : 185-196

藥物食品分析
第四卷 第三期

Regulatory Aspects of Living Biological Material

SHUNG-CHANG JONG* AND JEANNETTE M. BIRMINGHAM

American Type Culture Collection, 12301 Parklawn Dr., Rockville, MD 20852-1776 U.S.A.

ABSTRACT

Any living biological material is, in effect, a biotechnology factory complete with sophisticated process designs and its own source of venture capital. Biotechnology is the application of living material and its process system to obtain useful products or services. It is not limited to the recent developments in recombinant DNA techniques, monoclonal antibodies, and related processes and products, aspects with which it is most often identified, but includes the manufacture of nonrecombinant biological material, such as microorganisms and plants and animals from traditional breeding methods; biologically active compounds; and a variety of foods and drugs. Due to complex economic, social, and technological changes, biotechnology is in a state of transition from a knowledge-building science to a new industry. Among the many issues and concerns contributing to this is the emergence of ownership and intellectual property rights of biological material. Since the biotechnology industry is becoming increasingly global in nature, competition in world markets requires that special attention be paid to regulations concerning deposit requirements for patent purposes, transfer agreements, and the packing and shipping of biological material, both nationally and internationally.

Key words: Biological material, living organisms, biotechnology, intellectual property rights, patent deposit, transfer agreement, packaging, shipping.

INTRODUCTION

Biotechnology is the application of scientific and engineering principles to the processing of materials by biological agents to provide goods and services. Since ancient times, living organisms have been used to make beer, wine, cheese, bread, pickles, and sauerkraut; to ret flax; to age tobacco; to treat leather; to produce silage; and to digest sewage. Living organisms are able to perform a host of chemical reactions, such as oxidation, reduction, condensation, esterification, amination, deamination, phosphorylation, hydrolysis, decarboxylation, methylation, acrylation, and dehydration. As a result, they produce a wide variety of chemicals and drugs, such as alcohols, ketones, fatty acids, amino acids, enzymes, steroids, vitamins, and antibiotics.

Therefore, biotechnology is not limited to the recent developments in recombinant DNA techniques, monoclonal antibodies, and related processes and products, with which it is most often identified, but extends to the manufacturing of nonrecombinant biological materials, such as microorganisms, plants, and animals that are the products of traditional breeding methods; pharmacologically or biologically active compounds; and a variety of foods and drugs. The U.S. Patent

Correspondence to: Shung-Chang Jong

Accepted for Publication: Mar. 12, 1996

and Trademark Office (USPTO) has broadly defined biological material as "all material that is capable of self-replication either directly or indirectly," whether living or nonliving. Examples of biological material capable of direct self-replication are bacteria, fungi (including yeasts), algae, protozoa, eukaryotic cells, cell lines, hybridomas, plasmids, viruses, plant tissue cells, lichens, and seeds. Examples of those capable of indirect self-replication when another self-replicating biological material is present, such as after insertion in a host, include viruses, phages, plasmids, symbionts, and replication defective cells[1].

Any living biological material is, in effect, a biotechnology factory complete with sophisticated process designs and its own source of venture capital. In the last 15 years, the field of biotechnology has grown from a knowledge-building science to a new industry with a major influence on society. Due to complex economic, social, and technological changes, however, the biotechnology industry is in a state of transition worldwide. Among the many issues and concerns contributing to this is the emergence of ownership and intellectual property rights of biological material. Like knowledge or information, living material can be reproduced easily and inexpensively, making it difficult to establish and enforce property rights. Nevertheless, patents are generally considered to provide strong, comprehensive legal protection for living material and, therefore, should be the cornerstone of any intellectual property protection strategy.

The purpose of this review is to summarize the various regulations that apply to living biological material and includes intellectual property rights, deposit for patent purposes, transfer agreements, the packing and shipping of biological material, and the special requirements for rDNA material. All of these issues are critical for competition in the global markets of bioindustry.

PROPERTY RIGHTS TO LIVING MATERIAL

The law recognizes two types of property: tangible property and intangible property. Biological material, physically transferred from one researcher to another, is tangible property and is distinguished from the intangible or intellectual property that results from inventions based on that material. In fact, the patents, trademarks, or trade secrets associated with the material may be owned, transferred, and litigated separately from the tangible property. Intellectual property is personal property, and, as such, the owner may sell or otherwise dispose of his interest in the property or may grant others permission to use it.

Scientific investigators routinely trade samples of biological material. While informal exchange has been going on for a long time and has undoubtedly contributed to the advancement of science and technology, the transfer of biological material is becoming exceedingly more problematic. Biological material was once in the public domain, that is, it belonged to the community at large, unprotected by patent or copyright, and subject to appropriation by everyone. As a result, biological material was accessible to the entire scientific community. Recently, the use or application of that same biological material may be judged an intellectual property right with legal protection granted by sovereign authority.

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. However, effective legal protection for living material is not universally available. In many countries protection is inadequate, and in others there is no protection at all.

U.S. STATUTES AND LEGAL DECISIONS CONCERNING INVENTIONS INVOLVING LIVING MATERIAL

In the United States, three federal statutes deal with intellectual property rights in inventions involving living material:

1) The Plant Patent Act of 1930 (PPA)
2) The Plant Variety Protection Act of 1970 (PVPA)

3) The Utility Patent Act of 1790 under 35 USC 101

The first two statutes, the Plant Patent Act of 1930 (PPA) and the Plant Variety Protection Act of 1970 (PVPA), give inventors and breeders of specific plant varieties certain monopoly rights. The protection granted by the PPA is only for a single variety of an asexually reproduced plant. The PVPA protects novel seed varieties of sexually reproduced plants other than fungi or bacteria. Although the PVPA is not formally part of the patent act and is not administered by the USPTO, it provides breeders an alternative to the utility patent system.

The PVPA was amended on October 6, 1994, to close such loopholes as the "farmer's exemption, whereby a farmer was allowed to sell saved seed to other persons for reproductive purposes." The exclusion of protection for first generation hybrids was also removed. In order for a variety to receive protection, it must be new, distinct, uniform and stable. Most observers believe that the amendments will strengthen the PVPA by incorporating the broadest legal definition of plant intellectual property rights in U.S. law.

Since 1980 three federal rulings have clarified the option of patent coverage for living material under the Utility Patent Act of 1790:

1) *Diamond v. Chakrabarty*, 1980

2) *Ex parte Hibberd*, 1985

3) *Ex parte Allen*, 1987

The first was *Diamond v. Chakrabarty* (447 U.S. 303, 206 USPQ 193, 1980). A microbiologist, Chakrabarty, developed a genetically modified bacterium capable of breaking down multiple components of crude oil. The USPTO rejected Chakrabarty's patent application on the grounds that microorganisms are products of nature, and as living things, they are not patentable subject matter. In its landmark decision the Supreme Court ruled that a live, man-made microorganism is patentable subject matter under 35 USC 101 as a "manufacture" or "composition of matter." After the Chakrabarty decision, biological material was no longer the common property of the world.

In 1985 the USPTO Board of Patent Appeals and Inferences ruled in *Ex parte Hibberd* (227 USPQ 443, Bd. App. & Inf., 1985) that a corn plant containing an increased level of tryptophan was also patentable subject matter under 35 USC 101. Since the Hibberd ruling, utility patents have been granted on plants, even though protection was already available under PPA or PVPA.

In *Ex parte Allen* (2 USPQ 2d 1425, Bd. App. & Int., 1987), the Board ruled that polyploid oysters were patentable subject matter. Subsequently, USPTO announced that it would henceforth consider nonnaturally-occurring nonhuman multicellular living organisms, including animals, to be patentable subject matter under general patent law.

DEPOSIT OF LIVING MATERIAL FOR PATENT PURPOSES

Full disclosure of an invention in the application for patent protection has three requirements: a written description, enablement, and the best mode known to the inventor at the time of the invention (35 USC 112). Full disclosure was relatively easy to meet in the earlier days of the U.S. patent system. It has become increasingly more difficult in the case of biotechnological inventions. 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. The living material itself represents the means of enablement and the best mode and must be made publicly available for the purpose of enabling the disclosure.

The practice of depositing living material in public depositories for patent purposes began informally in 1949, but the sufficiency of such deposits was not tested until 1970. After the decision of the Court of Customs and Patent Appeals for the Federal Circuit (58 CCPA 769, 434 F.2d 1390, 168 USPQ 99) in *In re Argoudelis*, the USPTO required that inventions in which recently isolated or man-made microorganisms or cell

lines are essential for enablement must be supported by deposit of the material in a culture collection.

The current regulations under which the USPTO will accept a deposit to satisfy full disclosure are found in the *U.S. Federal Register* of August 22, 1989, and became effective January 1, 1990. 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 later to the public without restriction after the patent issues.

Viability must be determined for each deposit. If the deposited material loses its ability to function or becomes contaminated during the pendency of the application or during the term of the patent, a replacement is allowed. A replacement or supplemental deposit made during the pendency of an application may be made for any reason. Where a patent making reference to the deposit is relied on during any USPTO proceedings, the USPTO applies a rebuttable presumption of identity between the original and the replacement deposit. After issuance of a patent, however, a replacement or supplemental deposit requires a certificate of correction. Thus, an applicant has greater latitude in replacing a deposit during the pendency of an application than after the patent is issued.

If deposited material is claimed in a patent, or if it is essential for enablement, the USPTO requires that all restriction on its availability to the public must be irrevocably removed when the patent is granted. One significant policy the USPTO has adopted is that it will accept commercial availability of a material as evidence that the material is known and readily available to the public, even when it is commercially available only through the patent holder.

The current U.S. deposit regulations do not require that a deposit be made prior to the filing date of the application, and under specified conditions the applicant may dispense with deposit altogether, as in the case of commercially available biological material. 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 at least 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[2,3].

BIOLOGICAL MATERIAL TRANSFER AGREEMENTS

A transfer of living material from a donor to a recipient can involve two types of transfer: technology transfer or development transfer. Both can consist of a transfer of intellectual property rights and personal property rights along with the transfer of biological material. Intellectual property rights include patents, trade secrets, and know-how; personal property rights include the right to use and replicate the biological material. The material in a technology transfer already has commercial value, while material acquired in a development transfer requires further R&D before commercialization. Because either of the two types of transfer may be involved, clear, and preferably separate, definitions of the nature and scope of intellectual property rights and of the nature of and identifying characteristics of the replicable biological materials should be set forth in the transfer agreement. Lack of such agreements can result in long, drawn-out litigations.

The transfer agreement should clearly state that the provider has title to the biological materials being transferred, including clear title to any patents and pending applications or know-how involved. The agreement should define what existing patent rights and existing patent applications are included and define whether full title to these biological materials and all parts thereof and, potentially, title to products produced from the biological materials, title to derivatives, variants, mutants, improved DNA constructs, vectors, transformants are also included. In some instances, the provider may clearly wish to lease the biological materials, and no transfer of title to the recipient occurs. It should set forth whether the recipient is granted exclusive rights or non-exclusive rights to the transfer. Full ownership rights and the ability of the provider to transfer them for use may be more important than any intellectual property rights involved in the transfer.

Rights of materials transferred can involve territorial restrictions or field of use restrictions. Geographic limitations as to particular countries or areas of the world are permissible under U.S. antitrust principles, if they are a result of the exercise of valid patent rights. Field of use restrictions, that is, where a transfer of a biological material should limit its use, for example, to veterinary applications, human applications, to certain product types, or to certain markets, are legally proper and enforceable. The transferred rights should define whether the recipient will receive the full scope of rights, i.e., to make, use, offer to sell and sell, in all fields of use and in all territories, or whether any restrictions on any of these activities, or restrictions as to certain territories or restrictions as to fields of use exist. Field of use restrictions often are beneficial in biotechnology licensing where the biological material to be transferred has diverse uses[4].

REGULATIONS CONCERNING THE SHIPMENT OF LIVING MATERIAL

Because some biological material is pathogenic or of a hazardous nature, regulations concerning shipping are well defined by several U.S. federal agencies, including the U.S. Public Health Service, the U.S. Department of Agriculture, and the U.S. Department of Transportation. International shipments are governed by the rules and regulations of the U.S. Department of Treasury (Customs Service) and the U.S. Department of Commerce.

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 materials are sent by air, IATA regulations must be followed whether the flight is by Postal Service or freight carrier.

Scientists should be aware of the shipping and packaging requirements in their countries as well as in other countries. Illegal transport of biological material could result in incarceration and fines.

I. *U.S. Public Health Service*

Permit and license requirements depend on the type of pathogen (human, animal or plant) and the destination of the shipment. The federal government does not require a permit for every interstate shipment, because the large numbers of shipments make such regulations impractical. Those shipments that do require permits serve several purposes: 1) to ensure that the persons receiving the material are qualified to use them, and that they are properly prepared to do so; 2) to keep the government agencies informed about the volume of material that is being shipped and where it is going; and 3) to provide information about the shipment in the event of an accident during shipment.

According to the U.S. Public Health Service (USPHS) in the Code of Federal Regulations (42 CFR Part 72), a hazardous organism or etiological agent is defined as "a viable organism or its toxin that causes, or may cause, human disease." The USPHS requires a permit (CDC 0.753) for importation of such organisms into the United States. 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).

The USPHS designates organisms as Class I, II, III, or IV in *Classification of Etiologic Agents on the Basis of Hazard* (1974) and describes biosafety levels for infectious agents in *Biosafety in Microbiological and Biomedical Laboratories.*

1) Class I - materials with no recognized hazards require no special packaging;
2) Class II - materials with ordinary potential hazard are restricted to distribution to *bona fide* laboratories and require special packaging;
3) Class III - materials with special hazards require special packaging and a letter from the receiving institution acknowledging the hazard;
4) Class IV - materials with potential danger to health require a USPHS and/or USDA permit.

II. *U.S. Department of Agriculture*

Plant pathogens are described in 7 CFR 330.100 as organisms which "can directly or indirectly injure, or cause disease, or damage in any plant or part thereof, or any processed, manufactured, or other products of plants." The U.S. Department of Agriculture (USDA) regulates the movement of all plant pathogens and mycotoxin-producing strains across interstate or international boundaries and requires a permit from the Plant Protection and Quarantine Program (PPQ) for doing so. Form PPQ-526 (Application and Permit to Move Live Plant Pests) must be completed by the investigator who will receive the culture and submitted to the plant regulatory official of the state in which the culture will be used. The state in turn mails the form to PPQ for approval. These safeguards are set in place by USDA to protect the environment from pests and pestilence and by similar authorities in foreign countries.

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 regulations are stated in 9 CFR Part 122.2. 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).

III. *U.S. Department of Transportation*

The U.S. Department of Transportation (DOT) is responsible for establishing and enforcing regulations for safety aspects of transportation, which include, but are not limited to, infectious substances in domestic transport (49 CFR). The regulations cover 1) classification of material, 2) packaging, 3) hazard communication, 4) transportation and handling, and 5) incident reporting.

IV. *U.S. Custom Service*

The U.S. Custom Service regulates the importation of materials into the United States. It determines if materials are admissible and if they should be referred to other government agencies for examination, permits, and release. The Custom Service judges if import duties should be paid and if the packages being imported do, in fact, contain the goods that are manifested or declared.

V. *U.S. Department of Commerce*

The U.S. Department of Commerce (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. Material that does not require a validated license may be shipped under a general license (G-DEST). Institutions apply for this general license once and label each appropriate shipment as such. The DOC regulates the export for the following objectives, which are listed in the Export Administration Act of 1969, as amended: 1) to the extent necessary to protect the domestic economy from the excessive drain of scarce materials and to reduce the serious inflationary impact of foreign demand; 2) to the extent necessary to further significantly the foreign policy of the U.S. and to fulfill its international responsibilities; and 3) to the extent necessary to exercise the necessary vigilance over exports from the standpoint of their significance to the national security of the U.S.

There is a mandate for the DOC to identify organisms that might be involved in biological warfare and to place export controls on them. Several countries, such as Australia, New Zealand, and Germany also require import permits and licenses.

VI. *United Nations*

A United Nations (UN) Committee of Experts provides the international shipping regulations in "Recommendations of the Transport of Dangerous Goods." The current DOT regulations are based on the UN recommendations applicable to hazardous material transport in the U.S. Those who export biological material to foreign countries are required to follow the UN regulations. Mandatory requirements for shippers of dangerous goods to have a 24-hour emergency response number for hazardous material response have been in effect since 1990.

VII. *Canada*

In Canada microorganisms are assigned to one of four risk groups ranging from harmless to high community risk. Each risk group has a corresponding containment level. Containment level 1 is found in a basic microbiology laboratory, while containment level 4 represents a geographically isolated unit functionally independent of other areas. Agriculture Canada requires an annual import permit for all biological material shipped to Canada. Some pathogens require a single-entry permit; others can be shipped under a multipurpose permit. A plant quarantine permit is needed to export plant pathogens to Canada. As of September 1994, human pathogens require a Health Canada permit. Human pathogens that already require an Agriculture Canada single-entry permit now require both. Shipments of extremely hazardous agents require a Canadian Department of Transport Emergency Response

Assistance Plan.

VIII. *Europe*

The Working Party on Safety in Biotechnology of the European Federation of Biotechnology has classified organisms as harmless (EFB Class 1); low risk (EFB Risk Class 2), which may cause disease and might be a hazard to laboratory workers but are unlikely to spread in the environment; medium risk (EFB Risk Class 3), which offer a severe threat to the health of laboratory workers but a comparatively small risk to the population at large; and high risk (EFB Risk Class 4), which cause severe illness. Classes II through IV fall into special containment categories.

There has been some attempt at harmonization between the U.S. 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).

REGULATIONS CONCERNING THE PACKAGING OF LIVING MATERIAL

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 U.S. 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.

If sent by USPS, domestic shipments of etiologic agents must be sent by First Class Mail, Priority Mail, or Express Mail. Exceptions are those agents listed in 42 CFR 72.3 (f), which must be sent by Registered Mail or an equivalent system that notifies the sender when the package has been received. International shipments must be sent Registered Mail.

The USPS will accept only properly packaged biological material. Non-pathogenic material is placed in a foam insert, which is then put into a fiberboard cylinder. For freight carriers, the cylinder is further placed inside of a corrugated box. In the case of etiological agents or etiological agent preparations, the primary container (test tube, vial, etc.) with a volume of less than 50 ml must be securely sealed and watertight, and must be enclosed in a second, durable watertight container (secondary container). Several primary containers may be enclosed in one secondary container. Enough absorbent material must be placed between the two containers to absorb the contents of the primary container(s) in the event of leakage. For material shipped by freight carriers, the set of containers must be enclosed in an outer shipping container constructed of corrugated fiberboard, cardboard, wood, or other material of similar strength.

Etiologic agents are limited to 50 ml for both domestic and international shipments. When volumes of greater than 50 ml are shipped, a layer of shock-absorbent material must be placed between the secondary container and the outer container. Nonpathogenic material is limited to 1,000 ml per primary container, and the total volume in one outer shipping container may not exceed 4,000 ml.

According to 42 CFR Part 72, if material is shipped in dry ice, the ice must be placed outside the secondary container in such a way that the container does not become loose as the ice sublimes. Outer containers must be vented to allow carbon dioxide gas to escape. Dry ice cannot be used in international mail; material in dry ice must be shipped by freight carrier. If wet ice is used, it must be placed between the secondary container and the outer container. The outer container should be designed so that it does not collapse after the ice melts, and the entire package must be leakproof. Liquid nitrogen containers should be able to withstand ultralow temperature, and DOT regulations in 49 CFR Part 173.316

must be observed.

When transporting less than 50 ml of an etiologic agent by registered airmail, there are no specific requirements except compliance with the regulations on packaging. Shipping more than 50 ml of an etiologic agent requires special testing for the containers, and the material must be shipped only by cargo aircraft (DOT 49CFR 173.387). In addition to the required Biological Substance mailing labels and forms set forth by USPS, private shipping companies also require that a phone number be provided where a person knowledgeable about the shipment and its contents can be reached 24 hours a day. Living material, which is not acceptable for mailing to certain countries, is sent by freight carrier.

Several agencies require labels for etiologic agents or infectious substances, depending on the destination, the state of the shipment (dry or frozen), and the carrier (Postal Service or freight carrier).

All shipments of etiologic agents within the U.S. must carry the CDC etiologic agent label. Volumes of material greater than 50 ml must also carry a "Cargo Aircraft Only" label. If shipped by air freight carrier, shipments must have an IATA infectious substance label, a Shipper's Declaration for Dangerous Goods from the IATA, and be marked as UN 2814, Class 6.2, noting the name of the agent, volume, and the name and telephone number of the responsible party.

All foreign shipments of biological material regardless of hazard must have a Shipper's Export Declaration (DOC Form 7525-V). This document verifies the existence of a validated export license or a general license. If sent by the Postal Service (airmail only), biological material must also carry the green customs label (PS 2976) and a Cargo Aircraft Only label for volumes of culture greater than 50 ml. Etiologic agents must have the IATA infectious substance label, a Shipper's Declaration for Dangerous Goods, and be marked as UN 2814 with name of the agent, Class 6.2, volume, and the name and telephone number of the responsible party. A return receipt form is required for some organisms.

When a culture is shipped in dry ice, an additional IATA Miscellaneous 9 label and a UN 1845 marking with the amount of dry ice noted in kilograms is required. If the net weight of the dry ice is greater than 5 pounds, a Shipper's Declaration for Dangerous Goods is included. When the frozen shipment uses liquid nitrogen, the additional labels needed are an IATA nonflammable gas label, and "Do Not Drop", and "Handle With Care" labels. The words "Keep Upright" with arrows for proper orientation must be placed on each side or at 120° intervals around the package. The outer shipping container is marked Nitrogen, Refrigerated Liquid, Class 2.2, UN 1977[5].

REGULATIONS CONCERNING RECOMBINANT DNA MATERIAL

Ever since its introduction in the 1970's, 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.

I. *National Institutes of Health (NIH) Guidelines*

The first version of the NIH *Guidelines for Research Involving Recombinant DNA Molecules* was published in 1976 to provide a framework for conducting genetic engineering research in a manner that protected employees from infection and prevented adverse impact on the environment. Early guidelines prohibited large-scale cultivation of greater than ten liters of recombinant DNA-containing organisms. Subsequently, guidelines for large scale cultivation with three levels of containment and delegation of responsibility for review to the local Institutional Biosafety

Committee (IBC) were issued in 1980 and incorporated into the *Guidelines* as Appendix K in 1983.

In 1986 the European-based Organisation for Economic Cooperation and Development (OECD) published a report entitled *Recombinant DNA Safety Considerations*, in which appropriate physical containment practices for rDNA-containing organisms were described. The term Good Industrial Large-Scale Practice (GILSP) was introduced as a level of containment appropriate for non-pathogenic and nontoxigenic recombinant organisms. A rDNA-containing microorganism that meets the OECD criteria for GILSP is no more hazardous than those agents that have been used for decades to manufacture such products as antibiotics and enzymes. Accordingly, facilities and practices to achieve GILSP should be consistent with those used for traditional fermentations.

In 1991 a section entitled "Good Large-Scale Practice" (GLSP), similar to the OECD version from which it is derived, was added to Appendix K. GLSP is a level of physical containment that is recommended for large-scale research or production involving viable, non-pathogenic, and nontoxigenic recombinant strains derived from host organisms that have an extended history of safe large-scale use. Included were requirements for 1) a health and safety program, 2) well trained personnel; 3) facilities, clothing and practices appropriate to the risk of exposure; 4) discharges into the air, water, and soil that must be done in accordance with environmental regulations; 5) aerosol generation that must be kept to a minimum so that employee health is not adversely affected; and 6) a spill control plan. A comparison of GLSP to earlier large containment regulations reveals relaxation of certain requirements without any increase in risk to employees, the public, or the environment.

II. *Coordinated Framework for Regulation of Biotechnology*

In 1986 the United States Office of Science and Technology Policy (OSTP) of the Executive Office of the President accepted the concept of GILSP as national policy in its *Coordinated Framework for Regulation of Biotechnology*. It complements the NIH guidelines and allocates oversight responsibilities for biotechnology products. It lists the federal agencies from which approval must be obtained for commercial products and the research jurisdictions of each agency. Every effort was made to assure that regulatory responsibility for a product lies with a single agency. Responsibility for oversight is based on use, just as for traditional products. Existing statutes are viewed as being sufficient to establish jurisdiction over both research and products and to assure reasonable safeguards.

Foods, food additives, human drugs, biologics and devices, and animal drugs are reviewed or licensed by the FDA. Food products made from domestic livestock and poultry are under APHIS. APHIS also reviews plants, seeds, plant pests, animal pathogens and regulated articles, i.e., certain genetically engineered organisms containing genetic material from a plant pest.

Intergeneric-combination microorganisms containing genetic material from dissimilar source organisms and cultivated in a closed system are covered by the Toxic Substances Control Act (TSCA) and subject to the Environmental Protection Agency's (EPA) Pre-Manufacture Notice (PMN) requirement. EPA also reviews microbial pesticides, with APHIS being involved when the pesticide is also a plant pest, animal pathogen, or regulated article requiring a permit. When release into the environment is involved, jurisdiction depends on the characteristics of the organism, as well as its use. They must be reported to EPA under PMN requirements, with APHIS involvement as above.

An additional category of oversight is intrageneric combinations, which encompasses those microorganisms formed by genetic engineering through other than intergeneric combinations. APHIS has jurisdiction when the source organism is a pathogen and the microorganism is used for agricultural purposes. If it is used for non-agricultural purposes, it is within the realm of EPA with

APHIS involvement in cases where the microorganism is also a regulated article requiring a permit. Intrageneric combinations with no pathogenic source organisms are regulated by EPA, although EPA will probably only require an informational report.

III. *Regulation in the European Communities*

The current scheme for the regulation of biotechnology in Europe is based on the 1987 adoption of the Single European Act by the Commission of European Communities. Through this legislation, the 12 member countries have committed to the harmonization of employees' rights, living standards, and safety at work. Activities in Europe at this time include the adoption of three directives by the European Economic Community on 1) the protection of workers from risks related to exposure to biological agents at work, 2) the contained use of genetically modified organisms, and 3) the deliberate release of genetically modified organisms.

Two directives on the use of GMOs were adopted in April, 1990. They impose environmental controls on experimental and commercial activities with GMOs. The contained-use directive covers GMOs handled in physically, chemically, or biologically contained environments. This directive sets minimum conditions for containment and upkeep based on classification into two groups. Group I is for non-pathogenic organisms with poorly mobilizable genetic elements and a proven history of characteristics that provide for limited survivability and limited ability to replicate in the external environment. Guidelines for classification into group I were revised in 1991 to request more detailed information on the parental organism, vector, inserts, recipient, and the genetically modified organism that results from the process. Group II consists of all other GMOs. Specific containment measures for group II are based on the biological properties of the microorganism and the characteristics of the activity or operation in which it is used.

Deliberate release activities must be approved in advance of any actual release. A risk assessment of known or potential environmental impact is also required. Releases are allowed only under conditions of human and environmental safety that are as high as reasonably practical. Product release requires approval from the EC and the entire community. Ultimately European standards may become global standards[6].

IV. *Packaging and Shipping of Genetically Modified Organisms*

The packaging and international shipping of genetically modified microorganisms is regulated by IATA. According to the 1993 edition of the IATA List of Dangerous Goods Regulations, non-infectious genetically modified microorganisms "which are capable of altering animals, plants, or microbiological substances in a way not normally the result of natural reproduction" must be transported under UN 3245. Such items belong to hazard group 0 (Miscellaneous Dangerous Goods: same hazard label as for dry ice) and must be packed in accordance with Packing Instruction 913. Genetically modified microorganisms must be packed according to Packing Instruction 602 except that the packing need not be tested as provided for in Subsection 10.5. The maximum quantity in a primary receptacle must not exceed 100 ml or 100 g. Furthermore, genetically modified organisms, which are known or suspected to be dangerous to humans, animals, or environment must not be transported by air unless exempted by the States of origin, transit and destination[5].

REFERENCES

1. Burchfiel, K.J. 1995. Biotechnology and the Federal Circuit. p.545. The Bureau of National Affairs, Inc., Washington, DC, U.S.A.
2. Jong, S.C. and Birmingham, J.M. 1990. Disclosure Requirements for Biological Materials in Patent Law. Adv. Appl. Microbiol. 35: 256-293.
3. Jong, S.C. and Birmingham, J.M. 1992.

Patent Protection for *Aspergillus*-related Inventions. In Aspergillus: The Biology and Industrial Applications, J.W. Bennett and M.A. Klich ed., pp. 297-311. Butterworth Publishers, Stoneham, MA, U.S.A.
4. Gollin, M.A. 1995. Biological Materials Transfer Agreements. Bio/Technology. 13:243-244.
5. Brown, E.M. and Simione, F.P. 1994. ATCC Guide to Packaging and Shipping of Biological Materials. p.32. American Type Culture Collection, Rockville, MD, U.S.A.
6. Van Houten, J. and Fleming, D.O. 1993. Comparative Analysis of Current US and EC Biosafety Regulations and their Impact on the Industry. J. Industrial Microbiol. 11: 209-215.

生命物質相關之法令規章

鍾順昌* 珍妮伯明翰

美國標準菌種保存中心

摘 要

任何有生命的物質像一個小工廠，具有精密的運作系統，和潛在的產業資源。生物技術即應用此生命材料及其運作系統（即遺傳信息和生化功能）來製造有用的產物、造福人群。提到生物技術，人們對它的認識往往局限于新近發展的重組基因技術、融合瘤技術、及其相關之製造過程和產品，殊不知它是包括製造非重組生物物體諸如微生物、植物、動物，生理活性物質，以及各種化學品，醫藥品，飲食品和嗜好品。近年來，由於生產技術革新，經濟高度成長，以及社會急劇變化，生物技術已由知識積累科學邁向成為一新興工業。因此而造成了衆多問題，包括遺傳與生化資源之所有權和智慧財產權。現在生物產業多元化、自由化、國際化的發展，世界市場競爭要求我們要特別注意遵循生命物質相關的法令規章。這些法規的範圍包括專利生命物質的寄存、生命物質的移轉協定、和生命物質的包裝與郵寄托運。

關鍵詞：生命物質，活生物，生物技術，生物產業，智慧財產權，專利寄存，移轉協定，包裝，郵寄托運。