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The future of patent deposition of microorganisms?

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The deposition of patents of microorganisms in a culture collection recognized as an international depository authority (IDA) might be necessary in the realm of intellectual property rights. IDAs deal with various biological materials as well as microorganisms, and several problems are encountered in the handling and storage of such diverse samples, particularly in developing countries. IDAs also vary in the nature of the biological material accepted for deposition. An action plan for developing countries towards creating IDAs and preserving the natural gene pool has been evolved. It is likely that IDAs will transform into 'biological resource centers' and further into 'global common genetic resources', with an internationally agreed legal basis for benefit sharing.

Staying at the forefront of science with cutting-edge innovations and the need to protect such innovations have gained importance since the foundation of the World Trade Organization (WTO). Enriched by the tools of molecular biology, bioprocessing has a pivotal role in the production of biochemicals, bioenergy, biomedicines and bioremediation. In recent years, newer bio-industrial processes have been developed to tap the vast, invisible and still-to-be-explored reservoir of microbial diversity. Microbial resources used for these applications are preserved in microbial culture collections, which are essential for supporting scientific development both in the developed and the developing world [1].

The Uruguay Round agreement on trade-related aspects of intellectual property rights (TRIPS; Table 1) included microbial patenting as a component, and countries that have signed the agreement have to allow microbial patenting from the year 2005 onwards if it is not pre-existing [2]. Patent law requires disclosure of the full details of an invention. Descriptions and drawings are inadequate and insufficient if the invention involves the use of microorganisms or microbial components. Therefore, it has been agreed internationally that microbial samples must be deposited in a culture collection that is

Table 1. Useful URLs

Website	URL
Culture collections	
All-Russian Collection of Microorganisms	http://www.vkm.ru
American Type Culture Collection	http://www.atcc.org
Belgian Coordinated Collections of Microorganisms	http://www.belspo.be/bccm
Collection Nationale de Cultures Microorganismes	http://www.pasteur.fr/recherche/unites/Cncm/index-en.html
Collection of data on microbial resources of India	http://imtech.res.in/
Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH	http://www.dsmz.de/dsmzhome.htm
Japanese Federation of Culture Collections	http://wdcm.nig.ac.jp/wdcm/JFCC.html
Northern Regional Research Laboratory	http://nrrl.ncaur.usda.gov/
UK National Culture Collection (UKNCC)	http://www.ukncc.co.uk
UKNCC Members Organization	http://www.ukncc.co.uk/html/members/index.htm
US Federation for Culture Collections	http://usfcc.us
World Data Centre for Microorganisms (WDCM)	http://wdcm.nig.ac.jp/
WDCM Statistics	http://www.wdcm.nig.ac.jp/statistics.html
World Federation for Culture Collections (WFCC)	http://www.wfcc.info/aboutwfcc.html
Other organizations	
Comité Consultative des Centres de Ressources Biologiques	http://www.crb-france.org
G-77 Group of Developing Countries	http://www.g77.org/main/main.htm
World Intellectual Property Organization (WIPO)	http://www.wipo.org
Treaties and agreements	
Convention on Biochemical Diversity	http://www.biodiv.org/default.aspx
Convention on the Prohibition of Biological and Toxin Weapons	http://www.unog.ch/frames/disarm/distreat/bac_72.htm
Guide to the Deposit of Microorganisms under the Budapest Treaty	http://www.wipo.int/about-ip/en/budapest/guide/index.htm
Uruguay Round TRIPS	http://www.wto.org/english/tratop_e/trips_e/trips_e.htm

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recognized as an 'international depository authority' (IDA) within the framework of the Budapest Treaty on the international recognition of the deposit of microorganisms for the purposes of patent procedure (Table 1).

Of the 146 signatories to WTO, only 20 countries have a culture collection with IDA status (as of 4 April 2003). Thus, it is significant to analyze the modalities required for getting IDA status, as well as to identify the problems that will exist in countries without IDA status. Moreover, in accordance with the Uruguay Round TRIPS agreement, all of the developing countries must implement both microbial and product patenting from the year 2005 onwards. It is high time that developing countries discuss these implications and evolve strategies for effective implementation. In this review, we discuss the ways and means of meeting the requirements for acquiring IDA status.

WIPO and IDA status

An IDA has to be recognized by the World Intellectual Property Organization (WIPO; Table 1), a United Nations agency in Switzerland that is responsible for promoting the protection of intellectual property throughout the world. As of 21 January 2004, 179 states are members of WIPO. An intergovernmental organization to which several states have entrusted the task of granting regional patents and of which all the member states are members of the International (Paris) Union for the Protection of Industrial Property, or any depository institution can file with the Director General of WIPO a declaration in accordance with the Budapest Treaty and acquire IDA status. Furthermore, contracting states that allow or require the deposit of microorganisms for the purposes of patenting should recognize the deposit of a microorganism with any IDA.

For a depository institution to qualify for IDA status, WIPO has set some standard guidelines, including the following. The IDA should be located within the territory of the contracting state and should have a continuous existence with the necessary staff and facilities to perform its scientific and administrative tasks under the Budapest Treaty. The IDA must be impartial and objective. The IDA can accept any or specific types of microorganism, process and issue viability statements, provide cultures, perform training, identification, consultation and other services, and publish catalogues on holdings. The IDA should maintain secrecy and, at the same time, supply samples in accordance with the Budapest Treaty. The IDA should also collect, study and maintain both authentic strains of naturally occurring microorganisms and genetically modified strains that will help to conserve the microbial genetic pool for present and future generations. The list of strains maintained should be included in the World Directory of Collections of Microorganisms of the World Data Centre for Microorganisms (WDCM, located at the National Institute of Genetics, Japan; Table 1) for international reference and recognition.

World directory of collections of microorganisms

Scientists have long recognized the importance of culture collections in *ex situ* conservation (e.g. in zoos, botanical gardens and culture collections, where biodiversity is maintained in manmade or in contained conditions) and for the supply of authenticated microbial cultures, plant and animal cells and genetic elements. The need to compile microbial data and for data coordination at an international level resulted in the formation of the World Federation for Culture Collections (WFCC) and WDCM at the First International Congress on Culture Collections held in Tokyo in 1968 (Table 1). The Internet has circumvented the arduous labor involved in preparing an international catalogue giving details about each culture collection. The WDCM search engine can be used as a gateway to catalogues of various culture collections across the world. The software and methods used in preparing an electronic catalogue vary among different culture collections.

Achieving a complete network of electronic catalogues will be facilitated by the development of data standards and procedures to harmonize communication. Although 62 countries have registered in WDCM, so far only 20 have acquired IDA status. Compared with the total number of countries participating in WTO, WIPO and WDCM, this low number of IDAs also reflects the difficulties associated with their establishment. There are 473 culture collections registered in WDCM (as of 7 January 2004), of which 167 are supported by government, 33 are semi-governmental, 141 are supported by universities, 7 are supported by industry and 19 are private. Of the total collections, 172 produce catalogues of holdings and 2,499 people work in them (see WDCM Statistics; Table 1).

Defining microorganisms: an ongoing paradox

The use of the term 'microorganisms' has created considerable confusion. Generally, microbes or microorganisms are tiny living things that are invisible to the naked eye. For the purposes of patent protection, the term microorganism often applies to biological material including, for example, viruses, bacteria, actinomycetes, yeasts, filamentous fungi, mushrooms, protozoa, unicellular algae, cell lines of plants or animals, fused cells, transformants and vectors used in genetic engineering, variants, plant cells, DNA and RNA.

In many countries, there is uncertainty regarding the scope of the term 'microorganism'; furthermore, it is not possible to confine the term to only living things because culture collections deal with diverse biological materials. In fact, the European Union has decided to discontinue the use of the term 'microorganism'; instead, it has decided to use the term 'biological material', which means any material that contains genetic information and is capable of replicating itself or being reproduced in a biological system [3].

Challenges in deposition and the depositor's role

Although bacteria, viruses, fungi, plant cells, animal cells and so on differ marginally in the method and manner of their cultivation and storage, the basic facilities that are required are the same. Thus, culture collections can deal with various biological materials. At present, it is understood that IDAs are intended for storing any microscopic life form or microbiota (microscopic flora and fauna).

It is important that IDAs should demarcate naturally isolated microorganisms from genetically modified microorganisms to preserve the natural gene pool. Another

challenge is how to preserve the natural gene pool without the accumulation of spontaneous mutations and thereby to maintain the originality of the strains deposited. In addition, IDAs should be prepared to deal with the emerging need of microbial consortia (natural or artificial assemblages of interacting microorganisms), microcosms (natural or artificial sites that not only are defined completely in chemical and physical properties but are also gnotobiotics, that is, composed of known species that occupy ecological niches), and viable but not yet culturable microorganisms that might ultimately lead to the preservation of microbes that mimic the natural ecosystems. Such properties will pave the way for the transformation of IDAs into *in situ* culture reserves (places where biodiversity is maintained in nature, for example, ecological reserves, natural habitats and farms).

Notably, 99% of the existing microbial diversity has not yet been explored [4] and thus microbial handling, preservation and operation of IDAs will become more challenging. It is also significant that IDAs need to store non-living biological materials such as oncogenes, plasmids, RNA and eukaryotic DNA that are replicable in biological hosts. They therefore need to acquire expertise in handling these materials. Owing to the continuous developments in the fields of rDNA, whole-genome sequencing and bioinformatics, dealing with these non-living biomaterials is an additional challenge.

A depositor intending to submit a biological material for patent deposition purposes should have clear knowledge of the operation method of the intended IDA, as well as the requirements of a depositor (Box 1) in accordance with the Budapest Treaty. It is important for the depositor to ascertain whether he/she can meet the cost and the contracts, as well as the regulations and other modalities, of the IDAs.

Principal IDAs and their *modus operandi*

The US Federation for Culture Collections represents culture collections in the United States and two of its member collections, the Agricultural Research Service Culture Collection (at the Northern Regional Research Laboratory) and the American Type Culture Collection, are recognized as IDAs (see Table 1 for all culture collection websites). The UK National Culture Collection is coordinating the activities of the eight national collections in the United Kingdom, six of which have acquired IDA status. Russia holds three collections with IDA status. The Japanese Federation of Culture Collections consists of 23 culture collections, one of which has acquired IDA status.

The Belgium Coordinated Collections of Microorganisms is a consortium of four complementary research-based culture collections and is the only IDA in Belgium. It is a forerunning example in which several institutes within a country have been linked to form a distributed network of collections and have acquired IDA status as a common platform. The Collection Nationale De Cultures De Microorganismes at the Institut Pasteur, Paris, and the Deutsche Sammlung von Mikroorganismen and Zellkulturen GmbH are the only IDAs in France and Germany, respectively.

Box 1. Making a deposit with an international depository authority

Information a depositor must know before deposition

- Requirements for furnishing a new deposit or converting a previous deposit into a patent deposit.
- Types of microorganism accepted.
- The state in which the cultures (e.g. lyophilized, frozen, liquid suspension, agar slant) need to be submitted.
- The minimum number of replicates and minimum titer required for each culture.
- The time needed by the international depository authority (IDA) to carry out viability tests.
- The manner in which IDA replenishes diminishing stocks.
- The official language of communication.
- Information about the different kinds of contract between the IDA and the depositors.
- Import and/or quarantine regulations.
- Forms that must be completed and that would be issued by the IDA as official notification.
- Details that must be given in advance of deposition.
- Requirements for any special transport and/or delivery arrangements.
- Whether the IDA advises third parties of the correct procedures to be followed to make a valid request.
- Whether the requesting party must meet any health and safety requirements.
- Whether the samples furnished by the IDA are from its own preparations or from those supplied by the depositor.
- The fees payable under and outside (e.g. safe deposits) the provisions of the Budapest Treaty.
- The availability of a detailed guidance booklet from the IDA.

Important facts for a deposit as prescribed by the Budapest Treaty

- A deposit with an IDA is recognized as valid by all contracting states of the Budapest Treaty.
- Storage time is at least 30 years.
- After deposition, the culture cannot be claimed back.
- The depositor should himself keep samples of the culture for the same period of time so that the depositor can replenish the stock if, for any reason, the culture is no longer available from the IDA.
- The IDA is obliged to keep secret the fact of a deposit and the nature of the deposited material.

The general procedure followed by an IDA in accepting a deposit is outlined in Figure 1. When an organism is deposited in the IDA, some basic information must be provided with the application, including complete scientific name, source of isolation, geographical location, pathogenicity, and any known associated hazards, among others. For genetic materials, the name of the organism from which a vector, clone or library is derived must be included. For clones and constructs, the source of the DNA insert must be identified by species (e.g. human or mouse) or by scientific name if it is a microorganism or virus. When the source of the DNA is a microorganism or virus, the name of the gene and the identity of the host organism must be provided.

An analysis of the type of microorganism accepted by the recognized IDAs (Table 2) highlights wide variations in their ability to handle diverse life forms. In general, non-pathogenic bacteria and fungi and plasmids in hosts are accepted by most, whereas pathogenic forms, cell cultures, hybridomas and non-living biological materials such as oncogenes, RNA, plasmids and DNA strands are accepted

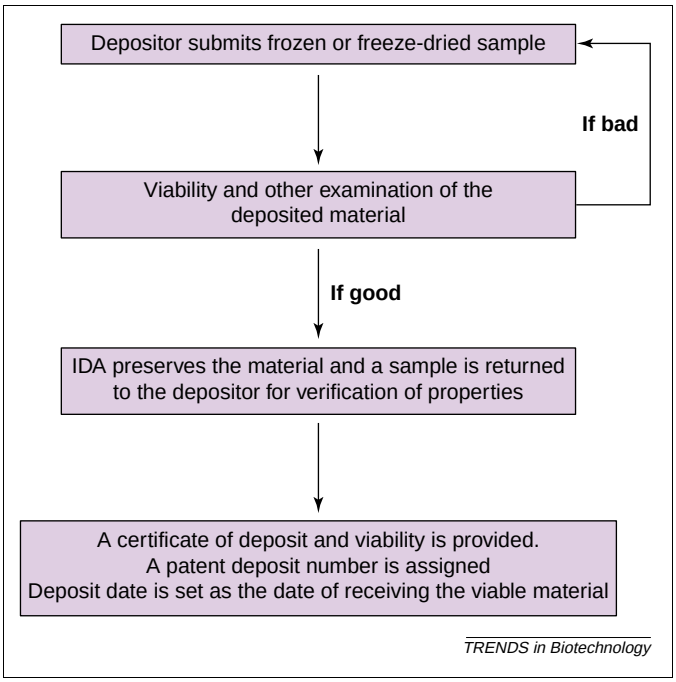

Figure 1. General procedure followed by an international depository authority. After submission, a sample is tested for viability. Good samples are preserved, and the depositor verifies the biological properties. A certificate of deposit and viability is issued along with a patent deposition number. The deposit date is recorded as the date that the sample was received.

only by some, owing to a lack of essential requirements such as facility back-up, technical know-how or skilled manpower. The technical challenge faced by the culture collections is to preserve the life form without any genetic changes for a long period of time (30 years), and only some microorganisms are amenable to preservation methods for long-term storage.

The risk associated with pathogenic forms and the biological 'dual use goods' – goods and technology developed for civilian uses that might also be used for military applications – are manifold. The danger is heightened because the method of supplying cultures includes these 'dual use goods', which could conceivably be used to produce biological weapons [5]. Internationally, the Convention on the 'Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction' (Table 1) prohibits the deliberate use of a disease agent as a weapon against humans, animals and plants. Culture collections are responsible for evolving regulations such as export licenses and for denying the supply of dual use microbes for customers who are suspected of making illegitimate use of them. But biological materials are also exchanged outside culture collections by scientists themselves, and thus care should be taken to avoid the threat of bioterrorism.

Table 2. Types of 'microorganism' accepted by some of the principal international depository authority

Country	International depository authority	Microorganisms accepted
Belgium	Belgium Coordinated Collections of Microorganisms (BCCM)	Animal cell cultures, bacteria (pathogenic and non-pathogenic), fungi (pathogenic and non-pathogenic), human cell cultures, hybridomas, oncogenes, plasmids (In hosts and not in hosts), RNA, yeasts (pathogenic and non-pathogenic)
Germany	Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH (DSMZ)	Animal cell cultures, bacteria (non-pathogenic), bacteriophages, fungi (non-pathogenic), human cell cultures, murine embryos, plant cell cultures, plant viruses, plasmids (in hosts and not in hosts), yeasts (non-pathogenic)
Japan	International Patent Organism Depositary (IPOD)	Algae, animal cell cultures, non-pathogenic bacteria, embryos, non-pathogenic fungi, plant cell cultures, plasmids (in hosts and not in hosts) non-parasitic protozoa, seeds, and non-pathogenic yeasts
UK	Culture Collection of Algae and Protozoa (CCAP)	Algae, non-parasitic protozoa
	European Collection of Cell Cultures (ECACC)	Animal viruses, animal cell cultures, bacteria (pathogenic and non-pathogenic), eukaryotic DNA, hybridomas, plant cell cultures, protozoa (parasitic and pathogenic), pathogenic yeasts
	CABI Bioscience, UK Centre	Non-pathogenic bacteria, non-pathogenic fungi, non-pathogenic yeast
	National Collection of Type Cultures (NCTC)	Pathogenic bacteria and plasmids (in hosts)
	National Collection of Yeast Cultures (NCYC)	Plasmids (in hosts) and non-pathogenic yeasts
	National Collections of Industrial, Food and Marine Bacteria (NCIMB)	Bacteria (pathogenic and non-pathogenic), bacteriophages, plasmids (in hosts and not in hosts), seeds, non-pathogenic yeasts
USA	Agricultural Research Service Culture Collection (Northern Regional Research Laboratory)	Bacteria (non-pathogenic), fungi (non-pathogenic), molds, plasmids (in hosts), non-pathogenic yeasts.
	American Type Culture Collection (ATCC)	Algae, animal viruses, animal cell cultures, bacteria (pathogenic and non-pathogenic), bacteriophages, embryos, eukaryotic DNA, fungi (pathogenic and non-pathogenic), human cell cultures, hybridomas, molds, murine embryos, mycoplasma, oncogenes, plant cell cultures, plant viruses, plasmids (in hosts and not in hosts), protozoa (parasitic, non-parasitic and pathogenic), RNA, seeds, yeasts (pathogenic and non-pathogenic)

Status in developing countries

Only eight countries in the G-77 group of developing nations (table 1) have signed the Budapest treaty so far, and only three of those eight have acquired IDA status (China, India and the Democratic People's Republic of Korea). It must be feasible for non-IDA countries to form a distributed network of culture collections similar to the Belgium Coordinated Collections of Microorganisms. For this, culture collections in developing countries must be upgraded in terms of

- legal framework and intellectual property rights regulations;
- administrative backup;
- ability to handle diverse microorganisms and/or their components;
- facilities for culturing, viability testing, preservation and safety with the required scientific knowledge and skilled personnel;
- extensive research and development set-up;
- providing consultation and other services including training.

In addition to the culture collections listed in WDCM, there are numerous culture reserves in universities, research institutes and private firms in every country. In this context, the program on the 'Collection of data on microbial resources of India' supported by the Department of Biotechnology, Government of India, under the aegis of the National Bioresource Development Board is a step forward (Table 1).

It is important that developing countries initiate several actions (Box 2), and it is possible for neighboring countries in a region with a common umbrella (e.g. countries participating in the South Asian Association for Regional Cooperation) to set up a common IDA, thereby sharing their resources and expertise and minimizing their burden in terms of financial support and availability of technical know-how. Although a depositor can deposit a culture in any IDA belonging to any country, if a national IDA is available in the country of patent origin, the cost will be more affordable, particularly for those in developing countries. Moreover, the possession of national IDAs will intensify international coordination and preservation of the natural gene pool of the country or region.

Box 2. Action framework for developing countries to acquire international depository authority status

(i) Identify the centers that are specialized in a specific category of microorganism, such as bacteria, fungi, viruses, agricultural microorganisms, cyanobacteria, plant and animal pathogens, algae or animal cell line, and form a coordinated culture consortium like Belgian Coordinated Collections of Microorganisms.
(ii) Develop a network of culture collections, launch website and link with international websites related to culture collections, and provide a wealth of information with a clear cut *modus operandi*.
(iii) Develop a web-based directory of cultures with culture collections combined with the provision of online searching and ordering.
(iv) Generate financial resources with a continuous flow of funds. Means of income generation can be augmented, but the following resources should be ventured for core funding:

- government support;
- private industrial support for, or participation in, functioning of the IDA;
- public and private foundation support;
- public fund raising;
- sale of biological resources and technical materials;
- provision of specialist services and technical consulting expertise;
- research income (e.g. grants and contracts);
- fee for repository services (e.g. for patent strain maintenance and safe deposits);
- provision of technical courses.

Future of IDAs

In the near future, IDAs might be replaced by 'biological resource centers' (BRCs); such centers will be the ultimate repositories because they aim to function also as information banks by compiling databases of molecular, physiological and structural information relevant to the collections, as well as related bioinformation [4]. The concept of BRCs came from worldwide work at the Organization for Economic Co-operation and Development; as discussed at the Tokyo Workshop on Biological Resource Centres, 1999: "BRCs are an essential part of the infrastructure underpinning life sciences and biotechnology". They consist of service providers and repositories of the living cells, genomes of organism and information relating to heredity and functions of biological systems. BRCs contain collections of culturable organisms (e.g. microorganisms, plant, animal and human cells), replicable parts of these (e.g. genomes, plasmids, viruses, cDNAs), viable but not yet culturable organisms, cells and tissues, as well as databases containing molecular, physiological and structural information relevant to these collections and related bioinformatics" [4]. BRCs must meet the high standards of quality and expertise demanded by the international community of scientists and industry for the delivery of biological information and materials. They must provide access to biological resources on which research and development in life sciences and the advancement of biotechnology depend [4].

France has constituted a consultative committee on BRCs (Table 1). Currently, there are four important issues under discussion by the committee: (i) scientific research on networks of genes involved in tissue and cell functioning and malfunctioning requires biological resources of guaranteed origin and quality; (ii) the diversity of biological collections and their uncontrolled emergence entail risks for health and for the environment (e.g. dissemination of pathogenic agents) and cause safety and security concerns; (iii) although there are legislative and regulatory frameworks for the scientific and economic use of biological collections, there are enforcement problems that have not yet been solved; (iv) the uncontrolled trade in biological samples, and the genetic history that is present in these materials, is in danger of being beyond any attempt at regulation. Biological collections are the key to postgenomic development and the industrial exploitation of scientific results. There are no measures to ensure that trade in this field is open and visible. In addition, the committee is studying the processes for assessing and accrediting BRCs to form a 'national network'. BRCs should also develop capacities to foster solutions to the issue of intellectual property rights, which

will be needed for individualistic depositors and collections.

Do all the countries have the essential political, economical and social backup to live up to this challenge? Sustained financial support and technical know-how for handling diverse microorganisms in line with safety requirements are some of the chief impediments faced by developing countries. Ultimately, we should progress towards evolving 'global common' genetic resources in which all the bioresources of this planet will be pooled, maintained and preserved at a universal node of a BRC. It should be created by the unified approach of all of the member countries of WTO with a legal basis for sharing the benefits with the country that originated of such knowledge. Benefit sharing should be based on commercial utility under the ambit of the Convention on Biological Diversity (Table 1). This will save effort and expenditure in creating such IDAs and BRCs in every country.

Concluding remarks

The aim of posterity and global betterment through the deposition of microorganism patents thus encounters several limitations. It is time to maximize efforts to increase the number of IDAs and to augment preservation of the natural gene pool. The need for IDAs and the pertaining procedures should be familiarized among the beneficiaries. It is important to intensify research to solve the problems associated with culture preservation.

At present, it is difficult to imagine all of the problems that might arise over the long term during the operation of IDAs, and hence the discussion of potential issues by an expert committee at a global level is needed. It would be appropriate to include developing countries in the decision-making process because they are also principal stakeholders in biological resources. International cooperation among the culture collections must also be fostered. Finally, we should move towards creating a universally acceptable type of BRC and global common genetic resources.

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