# ADVANCES IN
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# Culture Collections and Patent Depositions[1]

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## I. Introduction

Man's exploitation of microorganisms over the centuries is a well-known fact. Within the last three decades, this exploitation has had considerable

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impact not only on the progress of microbiology and chemistry and their many subdisciplines but also on the legal profession.

Literally millions of strains of microorganisms have been studied, in varying degree, by researchers in industry, government, and academe in efforts to discover new products; to develop new processes for the production of microbial metabolites useful in medical, agricultural, and industrial applications; and to control food spoilage. As a result of these intensive studies, scientific contributions have been made in chemistry, biochemistry, microbial physiology, microbial taxonomy, and in both chemical and biological nomenclature.

Patent laws and regulations, allowing some degree of protection to the inventors or discoverers of new processes and metabolites, have led to the buildup of a large body of patent literature along with the scientific literature. Many microbiologists and chemists today must consider both kinds of literature to keep abreast of developments in their fields of specialization. The scientific merits of the patent system have been questioned from time to time; however, in our opinion, the system overall has led to considerable scientific progress. Nevertheless, much valuable information probably still lies hidden and unreported because of the patent system.

The steadily growing use of microorganisms has imposed new problems on the microbiologists, chemists, and patent examiners and attorneys involved. Microbiologists and chemists must consider both scientific law and juridical law in the conduct of their work. Whether he likes it or not, the microbiologist curator of a collection of "patent cultures" becomes involved with legal aspects of satisfying requirements of patent offices throughout the world so far as preservation, maintenance, and distribution of these cultures is concerned. Requests for cultures and questions about their availability make it necessary to examine records on particular strains to determine whether a U.S. patent has been issued or, if not yet issued, whether the depositor has indicated that the culture could be distributed prior to issuance of the patent. The very tone of questions that one receives regarding patent cultures requires the assessment of each case on an individual basis. Clearly, some of the questions that have been posed to us have had legal implications.

Although a number of papers addressed to problems concerning patent cultures have appeared, many deal with legal aspects rather than microbiological or chemical ones: Casida (*2*), Daus (*5,6*), Edelblute (*7*), Hayhurst (*15,16*), Kent (*21*), Kurylovich (*22*), Levy and Wendt (*23*), Neshatayeva and Kiselyov (*25*), and Stoy (*34*).

This paper describes how we have handled our "patent culture collection" and points out some problems from the viewpoint of the microbiolo-

gist, who must be aware not only of new developments in his own discipline, but also of possible national and international legal implications of his activities.

## II. History of Patent Culture Depositions

From the beginning, cultures deposited in connection with patent applications occupied a unique position because of various requirements for confidentiality, special records, and special handling. Today, most major collections have a "patent culture collection."

The practice of depositing microorganisms in culture collections other than those of the patent applicants apparently existed nowhere in the world prior to 1949. So far as we know, the first such deposition was made by the American Cyanamid Company, in August 1949, when company representatives brought cultures of strain Lederle A-377 of *Streptomyces aureofaciens* Duggar to Peoria. Arrangements were made to deposit this strain in our Collection (NRRL), now known as the ARS Culture Collection, and it was accessioned as strain NRRL 2209. Later, in May 1950, representatives of Charles Pfizer & Company, Incorporated, deposited cultures of *Streptomyces rimosus* Finlay *et al.*, accessioned as strain NRRL 2234. *Streptomyces venezuelae* Ehrlich *et al.* also was one of the first antibiotic-producing streptomycetes deposited in a major collection, the American Type Culture Collection (ATCC), apparently in response to patent office requirements. It may well have been the first culture so deposited. Although we do not know the circumstances of its deposit in the ATCC, the type strain A65 = P.D. 04745 is listed in the second known U.S. patent on chloramphenicol production as strain ATCC 10712. The application date for this patent was March 16, 1948, and the issuance date October 4, 1949.

Other companies then began depositing cultures of microorganisms in connection with patent applications in the ATCC; the Collection of the Institute of Microbiology, Rutgers University; and our ARS Culture Collection. Most of these depositions, if not all, were made in confidence. Our arrangements were made with the understanding that progeny of the cultures would be made available and distributed to bona fide requestors from the time of issuance of the U.S. patent(s).

Aside from the three collections mentioned, and although there is no legislation for the practice (*29,41*), other collections have become involved. Based on statements made in granted patents, the U.S. Patent Office recognizes deposition of cultures in a number of foreign culture collections, e.g., The National Collection of Industrial Bacteria (NCIB),

the Commonwealth Mycological Institute (CMI or IMI), and the Forest Products Research Laboratory (FPRL) in the United Kingdom; the Centraalbureau voor Schimmelcultures (CBS) in the Netherlands; the Research Laboratories of Hindustan Antibiotics, Ltd. (HACC) in India; and the Institute for Applied Microbiology (IAM), the Fermentation Research Institute (IFO), the National Institute of Animal Health (NIAH), and the Faculty of Agriculture Hokkaido University (AHU) in Japan, among others. These collections have been cited in U.S. patents with application dates in the last several years.

These depositions apparently were made to satisfy demands for complete disclosure of specifications in applications and, in retrospect, would seem to have solved the problems that (i) it is difficult to set down on paper how to isolate a particular microorganism from a sample (generally soil) so that one "skilled in the art," i.e., a competent microbiologist or perhaps a chemist, could *readily* obtain the microorganism from nature; (ii) there being no precise definition for many species of microorganisms, it is difficult to write a description that will permit a competent microbiologist to *readily and accurately* recognize a particular taxon; and (iii) without the proper microorganism the processes would be inoperative, and no amount of words ever could allow them to be operable.

The practice of patent culture deposition has continued over the years; the ARS Culture Collection now maintains a "patent culture collection" of more than 1000 strains, the great majority of which are Actinomycetales. U.S. patents covering the use of about one-half of these strains have been granted.

## III. ARS Culture Collection Policies

Because there are limited guidelines governing deposition of cultures of microorganisms in connection with patent applications (*4,14,21,46*), each collection has developed its own particular policies. Our practices are based on some legal advice, on guidelines published from time to time in various journals including the *Official Gazette* of the U.S. Patent Office, and on our own in-house experiences and policies. Such policies, of course, are subject to change from time to time. Within recent years, a number of new companies and organizations have entered the picture. Because some of these were unfamiliar with culture deposition practices, we have prepared a procedures and policies statement as a guide for prospective depositors who request this information. The latest revision is given below.

## Procedures and Policies for Deposition of Cultures for Patent Purposes in the ARS Culture Collection

The ARS Culture Collection serves as a depository for cultures which are involved in fermentation patents and, therefore, will be glad to receive such materials in connection with patent applications. When such a culture is received, it is assigned a number in the collection and is maintained thereafter in a living state. Immediately after receipt, a letter is written to the depositor advising of the number assigned and including one of the following statements:

Furthermore, insofar as is practicable in carrying out the business of the Department of Agriculture, we shall refrain from distributing this culture pending the issuance of the U.S. Patent to your company, with the exception, however, that access to this culture by other parties will be granted upon receipt of written authorization from your company specifying the name and the ARS Culture Collection designation (NRRL number) of the culture and identifying the party who is to receive it. (Restricted distribution.)

OR

As of this date, the subject culture(s) will be made available to anyone who requests the same. (Nonrestricted distribution.)

OR

With reference to 886.O.G. 638, progeny of this (these) strain(s) will be avilable during pendency of the patent application to one determined by the Commissioner of patents to be entitled thereto under Rule 14 of the Rules of Practice in Patent Cases and 35 U.S.C. 122. All restrictions on the availability of progeny of the strain(s) to the public will be irrevocably removed upon the granting of the patent(s) of which the strain(s) is (are) the subject.

Deposition of strains of microorganisms in the ARS Culture Collection in connection with patent applications affords reasonable permanency of the deposit and ready accessibility thereto by the public if a patent is granted.

Pertinent references concerning deposition of strains for patent purposes are: USPQ 157: 437–444 (1967); OG 848: 863–867 (1968); OG 849: 5–11 (1968); USPQ 168: 99–104 (1971); USPQ 169, No. 6: II–III (1971); and OG 886, No. 4: 638 (1971).

It is suggested that you seek advice from your attorney as to which type of statement you should use. The ARS Culture Collection letter then can be attached to the patent application for the Patent Examiner.

There is no charge for the deposit or maintenance of cultures.

The ARS Culture Collection is unable to accept for deposit strains of viruses and would have to carefully consider any request to deposit strains of bacteria, yeasts, molds, *Actinomycetales*, and parasitic agents listed in classes 2 and 3 of the U.S. Department of Health, Education, and Welfare's "Classification of Etiological Agents on the Basis of Hazard" and the U.S. Department of Agriculture's publica-

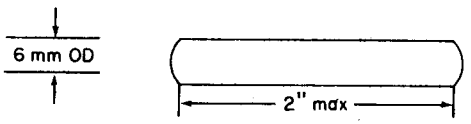
tions PA-873 and PA-967. Also we are unable to accept microorganisms that would be considered fastidious or mixtures of microorganisms which cannot be lyophilized. Potential depositors also should be familiar with the various U.S. laws and regulations regarding shipment and import of microorganisms.

The ARS Culture Collection does not issue a catalog or list. It has no regulations imposing restrictions on the use of such cultures deposited for patent purposes. Such materials are distributed according to the depositor's wishes which, in turn, generally are based on his interpretation of patent office requirements. Use of such materials, once distributed, is the responsibility of the requestor. Cultures are automatically removed from any restriction category, once a U.S. patent issues wherein the particular microorganism is involved.

Curators in the ARS Culture Collection do not attempt to make an identification or to name any organism which has been deposited in connection with a patent application, nor do they carry out research work with such deposits until a U.S. Patent issues or cultures are otherwise released. It is not necessary, of course, to provide a precise identification but the depositor should at least state to what genus the microorganism belongs. Also, if special media are required for its maintenance, the curators need to know this. Ordinarily, one or two agar slant cultures and one or two lyophilized preparations are received from depositors. Depositors also are responsible for resupplying material should the need ever arise and this responsibility extends beyond the life of the patent.

The depositor has the option of sending cultures for deposit in the ARS Culture Collection in three ways:

1. Thirty lyophilized preparations, clearly labeled with the depositor's original strain designation and preferably in tubes no longer than indicated in the drawing below:




One of these is checked for viability, the NRRL number placed on each tube, and the supply of tubes stored at 3 to 5°C. *Bona fide* letter requests for the culture would be shipped from this stock.

The ARS Culture Collection will no longer accept materials for deposit under option 1 unless they meet the specifications cited above. Larger sized tubes greatly complicate storage.

2. One lyophilized preparation, clearly labeled with the depositor's original strain designation. On receipt, the microorganism is cultivated on appropriate agar media and thirty lyophilized preparations made. One of these is checked for viability, the remainder handled as in option 1. This option, and option 3 below, is acceptable provided cultures submitted are not fastidious and do not require more than usual normal operating procedures.

3. One, or preferably two, agar slant cultures of the microorganisms growing on an appropriate medium. Sufficient material is prepared by our curators to make thirty lyophilized preparations, check one for viability and handle the remainder as in options 1 and 2. When the initial agar slant cultures deposited appear suitable, lyophilizations often are made from that material.

Cultures deposited in the ARS Culture Collection are considered as public property and the property of the ARS Culture Collection. Therefore, no strains

are removed, returned to depositors *in toto*, or completely destroyed except for very good reason, e.g., the receipt and accessioning of a virulent pathogen by mistake.

Progeny (agar slant cultures or lyophilized preparations) of strains of microorganisms deposited in connection with patent applications may be obtained (when restrictions, if any, are removed), free of charge by letter request stating the name of the microorganism and its strain number (either the depositor's number or our NRRL number) or by providing an otherwise satisfactory reference to the strain(s) in question.

We do not provide depositors with the names of requestors of microorganisms.

## IV. The Deposit

### A. Time of Deposit

Generally, cultures are accessioned in our patent culture collection on the day the deposit material is received and the depositor is so informed of the date. This procedure is based on the premise that the deposited material is, in fact, viable and authentic. In most instances the materials sent for deposit are viable. We have no knowledge of the relationship between the time of deposit of a particular strain and the date of the patent application. There has been no need for such information. The date of deposit, however, is of particular importance to depositors as exemplified in the latest guideline appearing in the *Official Gazette* of the U.S. Patent Office (*46*).

We do not authenticate cultures beyond simple generic or group (bacteria, yeasts, molds, Actinomycetales) placement. Sometimes, however, it may take as long as 1 month to grow cultures satisfactorily. Also, other responsibilities of our curators could delay preparation of materials for distribution stocks. These facts should be taken into consideration by the depositors in the event there might be a request for cultures within a short time of deposit. Such a circumstance conceivably could occur. It probably would be difficult for us to honor any request for material 1 or 2 days after receipt of the cultures for deposit. One could inoculate an agar slant of appropriate medium and ship it before any growth has occurred, but we look with disfavor on such a practice. To help resolve the problem of immediate requests, we will accept lyophilized preparations (30 such preparations is a reasonable and practical number) provided they meet certain physical requirements as indicated in our procedures and policies statement.

The practice of having the depositor lyophilize his own material in sufficient quantity for subsequent use in honoring requests also has other advantages. In the past, we have been accused of occupying a privileged position with regard to patent depositions because we, too, are engaged

in fermentation research. Access to active cultures would, of course, provide our curators with certain kinds of information. However, the so-called privileged position never can be escaped entirely, because records must be kept. The scientific integrity of our curators gives assurance that advantage is not taken of this position.

## B. Nature of Deposit

The kinds of materials we have received in connection with patent applications have ranged from cultures preserved in soil to lyophilized preparations. Generally, agar slant cultures are provided. In some instances the deposit of a single strain consists of an agar slant culture and a soil culture or an agar slant culture and one lyophilized preparation. In the letter accompanying the deposit, all materials should be clearly identified with the acronym (abbreviation, sigla) of the depositor's collection, a number designation in his collection, and the name of the organism. This has not always been the case. Occasionally, in the past, only the names of certain microorganisms were provided and, therefore, release of the cultures was obstructed. The same problem of appropriate delineation of microorganisms occurs in publications in scientific journals. When attempts to obtain release from the depositor for distribution of the culture fails, one other recourse is to check with the patent office regarding these cultures. Certain information in the applications may allow resolution. Otherwise, the particular cultures involved can be effectively restricted for years.

Occasionally, either obviously mixed or contaminated cultures are received. Receipt of such materials requires extra correspondence and work. Conceivably, legal questions could be raised. Because it often is difficult to pinpoint the origin of contamination, the competency of the depositor or of the curator can be questioned. In the case of accidentally contaminated cultures, legal questions as to whether the depositor or the curator was responsible could be raised. The 30-lyophilized preparation option would place the responsibility for culture purity with the depositor.

The use of deliberately mixed cultures for certain processes poses a different kind of problem. We are not prepared to accept such mixtures because the ratio of the components may be difficult to maintain. We can accept the individual components. If the components of such mixtures can be lyophilized and deposit of the mixture is preferred, the depositor is encouraged to prepare his own mixtures in proper ratio and exercise the 30-lyophilized preparation option.

The future may well hold more problems for curators insofar as the nature of deposits is concerned. New directions of microbiological and

chemical research have resulted in the appearance of more exotic and fastidious kinds of microorganisms as well as mixtures of microorganisms in processes. Further exploitation of the more commonly occurring, less fastidious, and easily isolatable microorganisms is becoming increasingly difficult. One might expect, then, that human, animal, and plant pathogens; extreme thermophiles or psychrophiles; diatoms; protozoa; nematodes; viruses; and cell lines of all kinds will appear among patent deposit strains in the years to come. Because of other responsibilities and because handling of these microorganisms falls outside their expertise or limitations, our present curators cannot work with such materials.

### C. Acceptability of Deposits

Because of the nature of the ARS Culture Collection and the missions and goals of the U.S. Department of Agriculture, the Agricultural Research Service, and our laboratory (the Northern Regional Research Laboratory), we currently are unable to accept certain microorganisms, particularly the viruses. Phages (bacterial or fungal viruses) are a possible exception. Processing of phages might be difficult, and we would prefer deposit of lyophilized phage and host preparations. Also, any request to deposit strains of bacteria, yeasts, molds, Actinomycetales, and parasitic agents listed in classes 2 and 3 of the U.S. Department of Health, Education, and Welfare's "Classification of Etiologic Agents on the Basis of Hazard" (40) and the U.S. Department of Agriculture's publications PA-873 and PA-967 (38,39) would have to be very carefully considered. We maintain liaison with the appropriate agencies in this regard. We do not plan to expand our operations in this direction.

Moreover, potential depositors should be aware of the packaging standards and permits for importation, exportation, and shipping of cultures required by the U.S. Public Health Service, the U.S. Department of Agriculture's Animal and Plant Health Division and Plant Quarantine Division, the U.S. Department of Commerce's Export Division, the U.S. Bureau of Custom's Import Division, the Department of the Army's Industrial Health and Safety Directorate, and other Federal and State agencies.

### D. Description of Material

When we receive only one agar slant culture or one lyophilized culture, it is our policy to prepare a number of lyophilized preparations of patent culture deposits as close, in number of generations to the original material as possible. Often, sufficient material is not available from the original slant culture alone. Therefore, it is necessary that our curators have

access to a reasonable description of the microorganism. Sometimes, only a generic name is sufficient. Occasionally, we receive lengthy taxonomic descriptions. We need only enough information to cultivate the microorganism appropriately and to recognize whether the culture is contaminated or mixed. We do not authenticate identifications of the organisms. Authentication would require a great deal of effort, particularly where yeasts, bacteria, and Actinomycetales are concerned. Many physiological tests would be required. Our curators accept the name given to the deposited microorganism until the U.S. patent has been granted, or until a nonrestricted culture has been sent to at least three requestors. After that time, the name of the microorganism is in the same scientific status as many others, i.e., subject to continuing changes in taxonomic concepts and in nomenclature. Thus, the original acronym and number (not the name) supplied by the depositor assume major importance as the only real fixed denominator so far as the history of the strain is concerned. Hopefully, most microbiologists are interested in describing their cultures and in naming them. One must remember, however, that the names are subject to change with the advance of science.

## E. Statement of Availability by Depositor

The availability and confidentiality of patent deposition cultures has been a matter of considerable concern to both foreign and domestic depositors and to the U.S. Patent Office. Some letters accompanying deposits are quite specific with regard to availability statements. Others say nothing in this regard. For the latter, we automatically assume that the culture is to be held in what we call "restricted status," i.e., progeny of the strain will not be sent to anyone other than the depositor or persons designated by him or the U.S. Patent Office, until the patent issues. Appearance of the name and our acronym (NRRL) and strain number in non-U.S. patents or other publications does not remove this restriction. We have received a number of letters requesting information on availability and confidentiality of deposits.

As a result of the controversy about availability of cultures and ensuing decisions by the U.S. Patent Board of Appeals and the Courts (*3,6,29,41–44*), we have had to recategorize our records on patent cultures. We now maintain three separate files; those on strains which are the subject of issued U.S. patents; those on strains deposited and accompanied with instructions that cultures be made available prior to grant of patent; and those on strains which are to be maintained in "restricted status" until grant of the U.S. patent.

An interesting series of letters concerning availability of cultures of

microorganisms (not necessarily directed to the patent culture problem) appeared in the American Society for Microbiology's News Letters in 1971 and 1972 (*8*). It is obvious from many of the letters that the special restrictions on economically important microorganisms apparently were either unknown or considered unimportant by some of the correspondents. Also of interest is the proposal (*13*) currently under consideration which may allow publication of U.S. patent applications prior to issuance of patents. This proposal, if adopted, could result in requests for patent cultures prior to issuance of the U.S. patent, or before the depositor has released the microorganism for distribution.

It should be remembered that patent culture availability during the pendency of a patent application is determined by the Commissioner of Patents and the depositor (*46*). Because of the confidential nature of applications, the only persons privy to the name, acronym, and strain number of microorganisms are the depositors and their attorneys, certain personnel in the U.S. Patent Office, and the curators of the collection wherein the culture is deposited. Therefore, except for actions taken by these individuals, no requests for the culture could be initiated until the patent issues. Prior publication of the name, acronym, and strain number does sometimes occur when foreign patents issue or foreign applications are published before the U.S. patent is granted. However, in such cases we continue to restrict distribution until the depositor or the U.S. Patent Office communicates with us. Notification by depositors that the U.S. patent has been granted has been minimal. Justification for distribution of many strains which are the subjects of U.S. patents have been based on our routine scanning of the *Official Gazette* of the U.S. Patent Office. Unusual titles to inventions and the omission of acronyms and strain numbers has complicated this procedure. Inclusion of the acronyms and strain numbers in the *Official Gazette* abstracts would help resolve this problem.

From a microbiological viewpoint, if information on the nature of a particular process were known, a microbiologist would like to have a culture or its description so that available files of information could be checked, or a selected number of cultures in his own collection could be screened to learn whether any produced the metabolites or carried out the process concerned. Except for interferences, such information and cultures are unknown to others in the field prior to appearing in print.

The U.S. Patent Office, with its complete knowledge of all U.S. applications and the legal requirements for making cultures available, is in the best position to publish the names, acronyms, and strain numbers of patent microorganisms and of the metabolites or processes involved. Such publication would provide a measure of relief because the informa-