CHAPTER 14

Patent Deposition of Microorganisms: Agricultural Research Service

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A microbial invention must be disclosed in a patent application in accordance with the requirements of the Patent Law. A patent applicant has complied with requirements for an adequate disclosure of a microorganism when he deposits it in a collection affording permanence of the culture and ready availability when the patent is granted. The Agricultural Research Service (ARS) Culture Collection serves as a repository for cultures connected with patent applications, and as such has issued guidelines which outline the responsibilities of both the depositor and the Collection. The depositor is responsible for submitting viable microorganisms in a prescribed manner, providing sufficient information to permit culturing of the microorganisms if necessary, and issuing statements concerning availability of the deposited cultures. The Collection is responsible for preserving, storing, and distributing the microorganisms during the duration of the patent. Finally, it maintains records and correspondence related to each patent organism. All information corcerning culture depositions is treated as confidential.

INTRODUCTION

A microbial invention, as any invention, must be disclosed in a patent application in accordance with the requirements of the Patent Law. The patent application must provide sufficient description to enable those skilled in the art to practice the invention. According to the statutory requirements 35 U.S.C. 122 (1952), disclosures for an invention must describe the "best mode" of practicing the invention process at the time the patent application is filed in the Patent and Trademark Office (PTO). In applications involving microorganisms, the "best mode" requirement of the law includes the requirement that the best culture of a microbe must be characterized taxonomically in the patent application, and it must be deposited in a suitable culture depository prior to filing the patent application (Saliwanchik 1976). If the best culture is already known and available to the public, deposition and description are not essential.

As a result of a key decision (In re: Argoudelis et al. 1970) by the Court of Customs and Patent Appeals, the PTO states that the following constitutes compliance with requirements of 35 U.S.C. 122 as an adequate disclosure of a microorganism to carry out the invention (Manual of Patent Examining Procedures 1977):

> "(1) the applicant, no later than the effective U.S. filing date of the application, has made a deposit of a culture of the microorganism in a depository affording permanence of the deposit and ready accessibility thereto by the public if a patent is granted, under conditions which assure (a) that access to the culture will be available during pendency of the patent application to one determined by the Commissioner to be entitled thereto under Rule 14 of the Rules of Practice in Patent Cases and 35 U.S.C. 122, and (b)

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that all restrictions on the availability to the public of the culture so deposited will be irrevocably removed upon the granting of the patent;

(2) such deposit is referred to in the body of the specifications as filed and is identified by deposit number, name and address of the depository, and the taxonomic description to the extent available is included in the specification; and

(3) the applicant or his assigns has provided assurance of permanent availability of the culture to the public through a depository meeting the requirements of (1). Such assurance may be in the form of an averment under oath or by declaration by the application to this effect.

A copy of the applicant's contract with the depository may be required by the Examiner to be made of record as evidence of making the culture available under the conditions stated above."

In the United States, the PTO recognizes the following culture depositories: American Type Culture Collection (ATCC); and the Agriculture Research Service (ARS) Culture Collection (NRRL). During the last several years, U.S. Patents have cited depositions in foreign 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 of 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. Evidently, the PTO also recognizes these foreign countries as suitable depositories for patent microorganisms. Because there are limited guidelines governing culture deposition in connection with patent applications, each depository must formulate policies that will not only accommodate the requirements of the patent regulations but also will fit in with the overall operation of the facility.

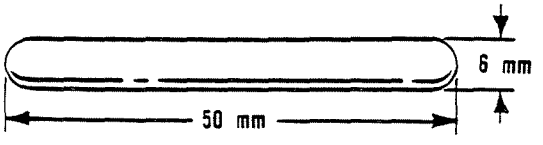
The ARS Culture Collection has based its procedures and policies for depositing patent cultures on some legal advice, on guidelines appearing from time to time in journals such as the *Patent Gazette* of the U.S. Patent Office, and on its own in-house experiences. These procedures and policies prescribe the responsibilities of the depositor and the ARS Culture Collection.

Discussion

Depositor's Responsibilities

The deposit. The depositor's prime responsibility is to submit pure and viable strains of the best cultures needed to practice the microbial process described in a patent application. Moreover, he is responsible for resupplying the cultures throughtout and beyond the life of the patent should the need arise. Three optional ways are available for submitting cultures to the ARS Culture Collection:

1. Thirty lyophilized preparations, clearly labeled with the depositor's original strain designation and preferably with dimensions indicated in the drawing below:



One is checked for viability; each remaining tube is marked with the NRRL number, and the supply of tubes is stored at 3 to 5 C. Bona fide letter requests for the culture would be shipped from this stock.

2. One lyophilized preparation, clearly labeled with the depositor's original strain designation. On receipt, the microorganism is cultivated on appropriate agar media and 30 lyophilized preparations are made. One of these is checked for viability, and the remainder are handled as in option 1.
3. One, or preferably two, agar slant cultures of the microorganisms growing on an appropriate medium. Sufficient material is prepared to make 30 lyophilized preparations. Viability check and storage are as described in option 1.

In the letter accompanying the organism to be deposited, the depositor should clearly identify each culture with the acronym (abbreviation, sigla) and number of his collection, and the name of the organism. Because organism names are subject to continuing changes in taxonomic concepts and in nomenclature, the original acronym and number (not name) supplied by the depositor assume major importance as the fixed denominator in the history of a strain. Sufficient information should also be given to enable the curators to cultivate lyophilized culture deposits and, if necessary, those cultures received on agar slants. With the information provided, the culture collection should be able to confirm that the deposited organism is pure and meets the general characteristics outlined by the deposit letter.

The appearance of mixed cultures, whether intentional or not, require added correspondence and work. In the case of accidental contamination, the question of responsibility can become a legal problem. The 30-lyophilized preparation option would place the responsibility for culture purity with the depositor.

Deposits of deliberately mixed cultures pose a problem because of the possible difficulty in maintaining the components in proper ratios. Consequently, the ARS Culture Collection discourages submission of such cultures for deposition. A solution is to deposit the individual components. If the depositor prefers to maintain the mixture, he is encouraged to exercise the option of sending 30 lyophilized preparations.

Statement of availability. The depositor should include in the letter accompanying his culture deposit a statement concerning availability of the organism before issuance of a patent. If no statement is made, the ARS Culture Collection assigns the culture to a "restricted status," i.e., until the patent issues, progeny of the culture will not be sent to anyone other than the depositor or persons designated by him or the U.S. Patent Office. Appearance of the name and our acronym (NRRL) and strain number in non-U.S. patents or other publications does not remove the restriction.

The letter advising a depositor that an organism has been accessioned also contains 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 available 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."

The patent applicant indicates which statement applies to the culture and then appends the letter to the application for the Patent Examiner.

Acceptability of deposits. The ARS Culture Collection hesitates to accept for deposition in the patent culture collection organisms that have fastidious or extreme requirements for growth or are pathogenic. Some examples are autotrophs; strict anaerobes; extreme thermophiles, psychrophiles, or halophiles; and organisms that have fastidious nutritional requirements. Because of other responsibilities and because handling of these microorganisms falls outside their expertise, our present curators cannot work with such materials.

We are not equipped to propagate, maintain, and process most viruses. Phages and fungal viruses are possible exceptions. Processing of phage might be difficult, so 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" (1972) and the U.S. Department of Agriculture's publications PA-873 (1970) and PA-967 (1971) would have to be considered carefully.

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.

Responsibilities of the ARS Culture Collection

Time of deposit. Generally, cultures are accessioned in the ARS Culture Collection on the day the deposit material is received and the depositor is so informed. The procedure is based on the premise that the deposit material is viable and authentic. Although the time of deposit of a particular strain is of minor importance to the Collection, it is of significant importance to the depositor. According to the Manual of Patent Examining Procedures (1977), a patent culture has to be deposited in a depository no later than the effective U.S. filing date of the application.

Accessioning of a culture does not necessarily mean that it is available for distribution. Difficulty in growing cultures and other responsibilities of the curators could delay preparation of a stock of lyophilized materials for distribution for as long as 1 month. In ideal

circumstances, we can prepare a stock of lyophilized material within 2 or 3 days after receipt of the culture for deposit. These facts should be considered by depositors in the event there is a request for cultures within a short time of deposit. To help resolve the problem of immediate requests, the depositor can use the option of sending 30 lyophilized preparations provided they meet the dimensional specifications described earlier.

Preservation and storage of microorganisms. One of the main responsibilities of the ARS Culture Collection is maintaining a store of viable patent cultures so that they are permanently available for distribution during the pendency and after the issuance of a patent. Of the several procedures used by the ARS Culture Collection to preserve and store cultures, lyophilization generally has been most effective (Raper and Alexander 1945; Wickerham and Flickinger 1946; Fennell et al. 1950; Haynes et al. 1955). The procedure is simple and requires a minimum of equipment. Other desirable features are the ease of storage and shipment of the rather small lyophil ampoules (6 × 50 mm).

After NRRL numbers are assigned and original records are prepared, the submitted materials are prepared for preservation by the appropriate curator. To yield sufficient material to produce 30 ampoules of lyophilized cells, cultures must be cultivated under conditions most likely to be suitable according to the information provided by the depositor.

Although the growth requirements for most organisms can be satisfied by routinely used conditions and media, the needs for certain strains may have to be determined by some small studies. Therefore, in situations where unusual organisms are concerned, recommendations from the depositor concerning cultivation conditions and media are welcome and useful. In addition to the viability check, it is also ascertained that each ampoule bears the proper NRRL number and date of preparation. Bona fide letter requests are shipped from this stock. Before a batch of preparation is exhausted, replacements are made by starting with materials from the existing lot.

When cultures are not amenable to lyophilization, they are preserved by periodic transfers on slants of appropriate agar media and stored in the cold or under sterilized oil. Because of its numerous deficiencies, the oil-overlay method is used sparingly at the ARS Culture Collection. Some of the deficiencies are: the medium dehydrates and the organism dies if the agar is not completely covered with oil; the transferring process is messy; hydrocarbon-utilizing microorganisms may attack the oil overlay; new agar slants must be prepared for a requestor; and the cultures are subject to all the problems associated with routine culture transfers, including run-down and loss of productivity.

Although other storage or preservation methods are available, they are used very infrequently or not at all at the ARS Culture Collection. A very small number of cultures are preserved in sterile soil. We do not use the deep freeze or liquid nitrogen for culture preservation.

To preclude losses due to natural disasters or other calamities, the Collection maintains a duplicate and separately stored collection of the considerable number of valuable patent and nonpatent microorganisms.

Viability check and characterization. As noted, the Collection routinely checks viability to establish the acceptability of each lot of 30 lyophilized preparations, including those made by depositors. If a complaint occurs, a viability check is made on another preparation from the same lot. Only rarely does the strain fail to grow. Therefore, we feel that a

recipient usually fails to revive a lyophilized culture because he lacks experience in handling such cultures or does not follow the directions accompanying each shipment.

In accepting and preserving deposits of microorganisms involved in patent applications, the Collection maintains the confidentiality of the information received by securing cell cultures and records, and by confining knowledge of the acronyms, names, and strain numbers only to the curator involved. Furthermore, the curators make only those observations necessary to assure that the deposited organism is viable, is pure, and meets the general characterisitcs outlined in the deposit letter. Most observations consist of macro- and microscopic examination of cultures growing in broth or on solid media. Consequently, checks on microorganisms concern taxa primarily above the species level. Observations are recorded only if difficulties are encountered and questions are raised.

Because of the confidential nature of patent organisms, the curators of the ARS Culture Collection do not conduct taxonomic or systematic studies of such organisms until the U.S. patent has issued and cultures have been supplied to at least three bona fide requestors. Depending upon their specific interests, curators may characterize particular cultures once they are available, one objective being the identification and naming of the microorganisms. As a result, the name may be changed and additional information on the strain may become available. Name changes should be proposed only after careful study, using the best and most contemporary criteria available. It should be realized that the Bacteriological Code does not recognize names of new taxa published in patents.

Records. Keeping records on the ARS collection of patent cultures alone takes considerable time and space. We maintain a separate file for each strain to facilitate information retrieval because the information and correspondence in these files frequently are needed to answer scientific, legal, or historical questions. Also, the files are carefully checked with each culture request to determine the availability status of the strain at that time. Release of restrictions on a patent strain is usually based on our scanning of the *Official Gazette* of the U.S. Patent Office. Oddly titled inventions and omission of acronyms and strain numbers frequently have complicated the scan. Inclusion of acronyms and strain numbers in the *Official Gazette* abstract would help resolve the problem. Better yet, our patent scan could be eliminated if all depositors would notify us when a U.S. Patent has been granted.

Conclusions

The ARS Culture Collection has a threefold responsibility in its patent-related culture collection operations: to the depositors of patent strains; to the general public, not excluding the scientific one; and to itself, as such operations affect its mission, goal, and research program. The procedures and policies of the ARS Culture Collection have been designed to help meet these responsibilities most effectively.

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