Maintaining Cultures for Biotechnology and Industry

Edited by
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MAINTAINING CULTURES FOR BIOTECHNOLOGY AND INDUSTRY

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Preface

One of the most valuable assets in any biological research organization, be it industry, academia, or government, is the culture repository. Whether one works independently in the laboratory, maintaining cultures for limited use, or as part of a larger, company-wide effort, the culture collection represents the heart of research efforts from basic and applied to development and manufacturing. Many companies have one or more well-staffed and equipped collections that serve different functions such as providing reference strains, assay strains, strains for screening purposes, and production strains. On the other hand, some small biotechnology companies or departments within universities may not be so well funded and supplied with appropriate equipment for maintaining these resources. In biotechnology companies and institutes, such as pharmaceutical, agrobiological, and biocatalysis, the research can often be quite focused or diverse in terms of "biodiversity" and include wild-type parent or reference strains and/or genetically engineered strains.

Maintaining culture traits, viable titers, and plasmids, in the case of recombinant strains, is important for stability of production strains, purity, and reproducibility of research. Most of the staff usually associated with culture collections are highly trained individuals who have the experience and expertise to identify and properly store or maintain cultures over long periods of time. Sometimes support is limited for culture collections in terms of lab space, staff, and monetary assets. This, in turn, may limit the method used to characterize, maintain, and preserve cultures. However, when a culture problem arises that may cost the company financial loss, major attention is usually given to the curator and his or her staff. The value that a curator and collection provides to research efforts is immeasurable and seldom fully appreciated.

With this in mind, we felt that a book addressing the various needs of maintaining and preserving the biodiversity within large and small biotech-

nological companies and institutions was necessary. In addition to the literature on maintaining cultures, techniques that have been passed on to graduate students or research associates by word of mouth and never published are included. The methods described are the product of the hands-on experience of our authors who have all worked with cultures in laboratories for many years. The readers will find it interesting to learn that there is more than one way to maintain cultures and that choices can be made based on equipment and budget considerations. It was also our intent that both students and experts in the field of maintaining cultures will find valuable use in the details given for simple preservation methods and in the references included, which provide additional information on maintaining each group of organisms addressed.

The authors have prepared a general introduction including discussions of biodiversity from a taxonomic or phylogenic point of view, an overview of classification, examples of economic or industrial importance, and information on characterizing cultures. Lists of culture repositories where strains can be acquired or deposited and references for more additional reading follow most chapters.

The book is organized into twelve chapters that cover the maintenance and preservation of algae, eubacteria, actinomycetes, fungi, protozoa, animal cells in culture, human and animal viruses, plant germplasm, plant viruses, and viroids. We begin with an introductory chapter on the importance of culture collections from a patent attorney's point of view. Also included in this chapter is a list of recognized culture collections for depositing patent strains under the Budapest Treaty. Subsequent chapters summarize the history and evolution of culture maintenance, and preservation techniques are described in detail. The final chapter suggests ways to evaluate and characterize cultures used for biotechnology and related industries.

Overall the book takes the mystery and fear out of maintaining and preserving cultures for biotechnology and encourages those both young and old to take pride in the job of being the "keeper" of the cultures. It can also be a valuable educational tool for managers to better understand the real value of culture collections and what is needed by curators to best maintain stability of cultures and reproducibility of desired traits for commercial profit. We believe this book will be a fine addition to the reference library of anyone interested in maintaining cultures for research.

Jennie C. Hunter-Cevera
Angela Belt

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CHAPTER 1

The Biological Deposition Requirement

Albert P. Halluin*

Introduction

As biotechnology ascends in significance in the overall scheme of modern innovation, mechanisms governing society's interaction with innovation have been forced to adapt to its particular characteristics. Given the enormous potential of biotechnology to benefit society, it is incumbent that industry, government, and academia continue to accommodate the special needs of this emerging field of scientific endeavor.

The establishment of depositories for biological materials and the development of specific sample preservation techniques have evolved in response to heightened interest in biological investigation. And as society seeks to ensure unfettered access to the perishable fruits of this research, the deposition and maintenance of organisms assume an even greater importance. By making available samples of established origin and quality, society may dramatically increase the efficiency of investigation. Existing cell lines and genetic materials may be made uniformly available to all researchers, providing a common starting point as well as a basis for comparison of the work of different groups.

*Partner, Pennie & Edmonds, Menlo Park, California. The author expresses his gratitude for the assistance of Kent Tobin in the preparation of this chapter. Mr. Tobin holds a Bachelor of Science Degree in chemistry from the University of California, San Diego, and is a graduate of the University of California, Hastings College of Law in San Francisco.

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At present there exist international depositories for biological entities, such as the American Type Culture Collection in Rockville, Maryland, the Fermentation Research Institute in Japan, the Centraal Bureau voor Schimmelcultures in The Netherlands, and the German Institute for Microorganisms (Halluin, 1982). Given the enormous variety of materials implicated in future biotechnological research, from unincorporated genetic material to antibodies to multicellular organisms, there is great need for uniform, detailed procedures regarding the care of such samples.

The purpose of this volume is to provide such guidance. By way of introduction, however, it is perhaps first useful to examine the motivation for deposition. In particular, the focus will be on the role played by the law in mandating public availability of biological entities that are the subject matter of a patent.

As of the writing of this chapter, the status of the requirement for making biological patent depositions is uncertain. Recent decisions handed down by the Court of Appeals for the Federal Circuit have significantly altered the long-standing policy favoring deposition (Halluin and Wegner, 1991; Halluin, 1992). The impact of this shift in philosophy has yet to be recognized fully, and cannot be underestimated given the importance of pharmaceutical research to modern society.

Concerns Other Than Patentability

Aside from the patentability concerns discussed below, there are many excellent reasons for maintaining depositories of available biological material. These include (1) the logistical convenience of a centralized storage location, (2) the security of maintaining backup samples should the working samples perish by mistake, (3) the advantage in safety conferred by ensuring that all who seek to obtain a particular material are adequately informed of its potential environmental and health risks, (4) the assured consistency in handling and preservation of samples within a particular depository, and (5) an enhanced ability to monitor the possessor and location of a particular sample at any given time (Hunter *et al.*, 1986).

This last rationale is especially important to the accurate assessment of issues such as licensing, trade secrecy, and patent infringement of a given composition, especially those provided by outside sources. The weight of these concerns will vary according to the purpose of the depository, but all can be envisioned as significant at some point in the life span of an average depository.

An Introduction to the Patent System

The patent system has its origins in the United States Constitution of 1789. Article I, Section 8, Clause 8 provides Congress with the power "[t]o promote the progress of science and the useful arts, by securing for limited times to authors and inventors the exclusive right their respective writings and discoveries." This intent has been explicitly elaborated and codified by United States Code, Title 35, whose provisions establish the Patent and Trademark Office as a division of the Department of Commerce.[1]

The effect of granting a patent is to assure the inventor a 17-year exclusive right to make, use, or sell an invention. Issuance of a United States patent is not a guarantee of such a monopoly; it merely creates a presumption of validity that may be challenged in court by a competitor.[2]

As with all legal doctrines, patent law is shaped and governed by underlying social policies, whose recognition is indispensable to understanding the operation of the law. There is commonly said to be one major policy disfavoring the granting of patents. This policy is the deeply rooted American antipathy to governmentally created and enforced monopolies. Thomas Jefferson, a noted inventor in his own right, strongly advocated the limiting of monopolies wherever possible, going even so far as to propose a provision in the Bill of Rights limiting the duration of any monopoly.[3] Although this provision was never formally adopted, the traditional American reluctance to interfere with the operation of a free market economy endures to the present day. This aversion is evidenced by the strictly limited duration of the patent term to 17 years or 20 years from filing.

Opposing the action of the antipathy to monopolies are two main policies. First is the incentive/reward rationale. This postulates that the granting of a period of exclusive sale is intrinsically beneficial to human creativity, because it provides an economic incentive to the inventor in the form of a monopoly over the sale of the product. This policy operates not only to reward the inventor, but also to prevent competitors from

[1]35 USCA §1. Establishment, reads in pertinent part:

The Patent and Trademark Office shall continue as an office in the department of Commerce, where records, books, drawings, specifications, and other papers and things pertaining to patents and trademark registrations shall be kept and preserved, except as otherwise provided by law.

[2]The legal effect of a presumption is to place the burden of persuasion on the party challenging validity. The judge or jury will commence their analysis from the proposition that the patent is in fact valid. The party opposing the patent must then provide evidence stating otherwise (Harmon, 1988).

[3]See *Graham v. John Deere Co.*, 383 U.S. 1, 8–9 (1966).