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Biotechnology Industry in the USA: Convergence of Scientific, Financial and Legal Practices

Terry C. Bradford

Abstract

The current biotechnology industry in the United States began twenty-five years ago and can be thought of as a process of co-production. Biotechnology industry in the United States has been shaped by 1) a pipeline of innovation for the continued development of new biotech products and services, 2) sources of financing willing to assume high risks and 3) the ability to secure strong intellectual property protection. In 1980, a convergence of these three events enabled the science of biotechnology to become a vibrant commercial enterprise.

Introduction

Science alone did not establish the biotechnology industry. There was a convergence of events in 1980 that resulted in the emergence of the U.S. biotechnology industry. This convergence enabled entrepreneurs and established commercial enterprises to secure intellectual property (patent) protection for biotechnology innovation, to acquire the commercial rights to intellectual property created in U.S. universities and to patent new life forms created by biotechnology methodologies. Without this convergence, commercial biotechnology would have evolved quite differently or not at all.

In 1980, three events occurred as a result of separated actions of each of the three branches of the United States government. The Executive Branch in the form of the Department of Commerce, U.S. Patent and Trademark Office issues patent No. 4,237,224, the Cohen-Boyer patent. The Legislative Branch, Congress and the Senate, enacted the Bayh-Dole Act, and the ruling of the U.S. Supreme Court in Diamond v. Chakrabarty. These three separate actions of the body politic converged in 1980 to enable high risk venture capital

investments in the emerging science of biotechnology. These investments launched a new industry that would become global in scope and profound in its impact on human health and its potential for humanity.

From science to industry

The word "biotechnology" conjures a spectrum of scientific discoveries, people and events that range from the characterization of DNA's double helix to the birth and death of a sheep named Dolly to the disputes over stem cell research. Biotechnology is generally thought of as two methodologies of molecular biology: recombinant DNA technology and hybridoma technology. The first recombinant DNA experiments were carried out in the early 1970's and the first hybridomas were created in 1975. More general, biotechnology is defined as any technique that uses living organisms (or parts of organisms) to make or modify products, to improve plants and animals or to develop microorganisms for specific uses.

If one looks at modern commercial applications of biotechnology, based on recombinant DNA technology, one finds a particular distribution in the use of recombinant organisms - new life forms to serve in the production of food and medicines and to solve environmental problems. This leads to the division of scientific application biotechnology methodologies and innovation into three general areas: Agricultural Biotechnology, Pharmaceutical Biotechnology, and Environmental Biotechnology. This essay will focus primarily on Pharmaceutical Biotechnology including human pharmaceutical proteins used in human therapeutic, vaccine and diagnostics as the example of convergence of events that led to emergence of a new commercial industry sector.

Human therapeutic, vaccine and diagnostic proteins are made in one of two ways: using recombinant DNA technology or hybridoma technology. In hybridoma technology, a B-lymphocyte secreting antibodies against a specific antigen is fused with a myeloma cell (a cancerous B-lymphocyte). The resulting cell if injected in a mouse's abdomen or if cultured in a bioreactor will grow and divide, indefinitely, producing large quantities of antibody which can then be harvested. The resulting proteins are called monoclonal antibodies (MAb) and are most often used in diagnostic kits. The most famous MAb containing diagnostic kit is the pregnancy test.

1 I addressed this issue elsewhere: Zwart (1995).

Large quantities of proteins can be produced using bioprocessing technology. Using the principles of biology, chemistry and engineering, processes are developed to create large quantities of proteins in an economical manner. A facility is built or adapted to house these processes. These processes include media and buffer preparation, upstream processing and downstream processing. All processes are monitored by quality control. Again the entire manufacturing process must take place in an atmosphere of current Good Manufacturing Practices (cGMP) which is the ISO 9000+ of the protein pharmaceutical industry. The Food and Drug Administration is the United States agency that oversees the cGMP regulations.

Between the evolution of ancient biotechnology techniques into today's modern biotechnology industry that uses recombinant DNA to create its products is a huge chunk of history that ranges from the isolation of DNA in 1869 by Friederich Miescher to the discovery of penicillin by Alexander Flemming in 1928. The modern science that started biotechnology was the discovery of the structure of DNA in 1953 by James Watson, Francis Crick and Rosalind Franklin. Many important events advanced that science such as the deciphering of the genetic code in 1961 by Marshall Nirenberg and H. Gobind Khorana, and the first recombinant DNA experiments that brought Paul Berg, Frederick Sanger and Walter Gilbert a shared Nobel Prize. The work of Kary Mullis and others at Cetus Corporation that led to the invention of a technique for multiplying DNA sequences in vitro by the polymerase chain reaction (PCR) has been called the most revolutionary new technique in molecular biology in the 1980s. Many have contributed to the evolution of biotechnology. However, Stanley Cohen and Herbert Boyer's discovery of recombinant DNA technology is considered to be the key event in the birth of modern biotechnology and what has become the U.S. biotechnology industry. (*Biotech Chronicles,* Copyright 1999)

US Venture Capital

For almost thirty years, U.S. venture capital has been the financial life blood of the biotechnology industry. Reviewing the evolution of modern U.S. venture capital environment is helpful to understanding how commercial biotechnology emerged. A convergence of Diamond v. Chakrabarty, the Cohen-Boyer patent and the Bayh-Dole Act in 1980 established the equity risk

environment necessary for the financial investments required to launch the biotechnology industry.

The current U.S. venture capital industry began taking shape in the post World War II era. In 1946, American Research and Development Corporation, was founded and become a pioneer venture capitalist. The American Research and Development Corporation investment in Digital Equipment provided it with an astounding 101% annualized return on investment. By the mid-1950's, the US government recognized the need for risk capital as an economic stimulus and established the Small Business Investment Companies (SBIC) program. US venture capital was beginning to be an organized high risk-high return investment alternative for wealthy individuals and families.

In the late 1960's and early 1970's the venture capital industry suffered a series of set-backs. After a strong IPO market brought over 1,000 venture financed companies to market in 1968, the public markets went into a seven-year slump. There were many disappointed stock market investors and a lot of private investors disenchanted with venture capital. Then, in 1974, Congress dealt a severe, though unintentional blow to the venture capital industry. In response to abuses of corporate pension funds (abuses that were unrelated to the venture industry), Congress passed ERISA -- the Employee Retirement Income Security Act. ERISA was intended to protect corporate retirees by curtailing the abuse of pension fund moneys. However, pension fund managers responded by halting their participation in all forms of high-risk investing. As a result of the poor public market and ERISA legislation, venture capital fund raising hit bottom in 1975. In that year, the *entire* industry raised a grand total of $ 10 million for new investment. But in that same year of 1975, a young venture capitalist named Robert Swanson initiate a dialogue with a researcher named Herbert Boyer who was faculty at the University of California at San Francisco. That discussion would lead to the formation of Genentech Inc. and to an inseparable linkage between the rise of U.S. venture capital and the biotechnology industry.

At this critical juncture, a number of events occurred that would position US venture capital to finance the biotechnology industry. First, there was a series of legislative and regulatory changes in 1978 that improved the climate for venture investing. Congress slashed the capital-gains tax rate to 28% from 49.5%. The Labor Department issued a "clarification" that eliminated ERISA as an obstacle to venture investing. These and other changes in government

policies encouraged high risk equity investing.

At the same time, there were a number of high profile IPOs by companies that had been launched by venture capital investments. These included Federal Express Corp. in 1978, Apple Computer Corp. in 1981 and Genentech, Inc. in 1981. Even though this rekindled interest in venture capital on the part of wealthy families, the shift from family wealth to institutional investments into venture capital funds was accelerating. Venture capital firms were becoming institutionalized and professionally managed.

In the 1980s, the venture capital industry began its greatest period of growth. Prior to 1980, wealthy individuals and families were the largest single source of capital, accounting for about a third of all funding. With the shift in the 1980s, institutional investors, e.g. public and corporate pension funds, insurance companies, banks, endowment funds and major corporations had by far become the most important source of venture capital funding. Since then, individuals and families have come to account for less than 10% of investments in venture funds. In 1981, the capital gains tax was further reduced from 28 percent to 20 percent. Again, the incentive for high risk equity investments through venture capital funds was increased. (Galante, *The Private Equity Analyst*)

The institutional investments in venture funds, the changes in government policies, (ERISA, capital gains, etc.) and the movement of venture funds away from family control and to professional management provided the high risk investments that capitalized on the "convergence" leading to the create the U.S. biotechnology industry. (Bradford, *Venture Capital and Biotech's Symbiotic Relationship*)

The "Biotechnology Patent"

In 1973, scientists for the first time successfully transferred deoxyribonucleic acid (DNA) from one life form into another. Stanley Cohen and Annie Chang of Stanford University and Herbert Boyer of UCSF "spliced" sections of viral DNA and bacterial DNA with the same restriction enzyme, creating a plasmid with dual antibiotic resistance. They then spliced this recombinant DNA molecule into the DNA of bacteria, thereby producing the first recombinant DNA organism. This discovery was published a year later in The Proceedings of the National Academy of Sciences. Cohen and Boyer demonstrated the expression of a foreign gene implanted in bacteria by recombinant DNA methods. They showed that DNA can be cut with restriction enzymes

and reproduced by inserting the recombinant DNA into *E coli.*

The invention of Herbert Boyer and Stanley Cohen's is the "biotechnology tool" now commonly known as recombinant DNA cloning or gene splicing. Under this technology, a gene from a piece of foreign DNA is inserted into a bacterial plasmid. The plasmid is inserted into a living organism, and the organism becomes a cell "factory" capable of reproducing the desired gene in unlimited quantities.

This technology became the core of the fledgling biotechnology industry. Based on its ownership of patented biotechnology, Stanford University licensed a total of 467 companies to use this technology for business purposes, i.e. the discovery and commercialization of new products. Products sold under the licensing program include tissue plasminogen activator for heart attacks, erythropoeitin for dialysis patients, insulin for the treatment of diabetes, growth hormone for children with growth deficiencies and interferon for cancer patients. Genentech was formed in 1976 based on these genetic engineering techniques and employed the methods to produce human insulin in *E. coli*. Other major licensees included Amgen, Eli Lilly, Johnson & Johnson, and Schering Plough. (Rowland, Bertram, *The Cohen/Boyer Cloning Patent*)

The Cohen-Boyer experiments were begun in 1973. The major patent to protect the recombinant DNA technology for commercialization was file in January 4, 1979. US Patent 4,237,224 was issued on December 2, 1980. Issuing of the Cohen-Boyer patent provided that commercial intellectual property protection necessary for the high risk investments required to leverage this science into profitable products. Without Patent 4,237,224 or a similar patent, commercial biotherapeutics as we know them today might not exist. (USPTO)

Bayh-Dole Act of 1980

The US economy is driven by technology innovation. The shift of the US economy from manufacturing to a technology economy has been driven by the information technology industry and the biotechnology industry. The information technology industry is based on silicon and software. The commercialization of information technology innovations of the 1970's and 1980's came more from the garage, e.g. Apple Computer, Microsoft and Lotus 123 than from corporate R&D and universities.

Biotechnology however is undeniably the child of innovations emanating from the research universities, institutes and academic medical centers. One

single event, the passage of the Bayh-Dole Act of 1980 transformed U.S. academia into the R&D engine of biotechnology. Without Bath-Dole (named after Senators Birch Bayh and Robert Dole), the biotechnology industry would have emerged differently in form, scale and timing.

Bayh-Dole is possibly the most inspired piece of economic legislation to be enacted in the US over the past half-century. Together with amendments in 1984 and augmentation in 1986, this single piece of legislation unlocked all the inventions and discoveries that had been made in laboratories throughout the United States with the help of taxpayers' money. Before Bayh-Dole, the fruits of research supported by government agencies had belonged strictly to the federal government. Nobody could exploit such research without tedious negotiations with the federal agency concerned. Worse, companies found it nigh impossible to acquire exclusive rights to a government-owned patent. And without that, few firms were willing to invest millions more of their own money to turn a raw research idea into a marketable product. More than anything, this single policy measure did more than anything else to mold the biotechnology industry as we know it today.

President Carter signed the Bayh-Dole Act (Public Law 96-517) in December 1980. Its main function was to standardize previously disjointed federal policy. Bayh-Dole took the decision about commercialization out of federal hands, insulating the process from political interference. With later amendments, it allowed non-profits to offer exclusive licenses, which provided the incentive for the venture capital industry to invest in unproven university technology, and it required the institutions to share proceeds with the inventors. Clarification of intellectual property ownership helped give companies and venture capitalists the confidence to make investments in unproven technologies.

The Bayh-Dole Act allows for the transfer of exclusive control of government funded inventions and technologies (intellectual property) to universities and businesses who are the recipients of government sponsored research and contracts. These universities and business can then commercialize the innovations through additional R&D investments or out-licensing to third parties for the purpose of further development and commercialization. Bayh-Dole reaffirmed that ownership and control of patents derived from federally funded research belonged to the performing institution, not to the sponsoring federal agency. The recipients of federal R&D dollars are then permitted to exclusive-

ly license patented inventions to other parties. The federal government, however, retains "march-in" rights to license the invention to a third party, without the consent of the patent holder or original licensee, where it determines the invention is not being made available to the public on a reasonable basis. The government has rarely exercised these march-in rights.

Before Bayh-Dole, inventions and discoveries made in American universities, teaching hospitals, national laboratories and non-profit institutions sat in warehouses gathering dust. Of the 28,000 patents that the American government owned in 1980, fewer than 5% had been licensed to industry. Although taxpayers were footing the bill for 60% of all academic research, they were getting hardly anything in return.

The impact of Bayh-Dole has been dramatic. Prior to 1980, only a handful of major universities had the resources and desire to fight the federal bureaucracy for months or years to obtain waivers to patent and own inventions. A trickle of university patents, 200 in 1980, has turned into a flood. Now more than 3,000 patent applications a year are filed by US academia. Academia's share of the total U.S. patents issued rose from a fraction of a percent prior to 1980 to 3 percent (and much more in certain classes of advanced technology). Overall, 166 institutions report nearly 13,000 active licenses to companies to commercialize patented inventions, a number rising by 1,000 or more every year. University R&D is responsible for the development of 44% of all new U.S. drugs and 37% of all new pharmaceutical processes. (Economist, Dec. 14, 2002)

The commercialization of university biotechnology innovation enabled by Bayh-Dole has produced billions of dollars of corporate revenue and royalties for academia. The Cohen-Boyer patent alone garnered more than 300 licensees and returned an estimated three hundred millions of dollars to the inventors' institutions and the inventors themselves. Only three years later, Columbia University obtained a patent on the co-transformation process, which extended recombination to enable the delivery of specific genes into mammalian cells. It has been used to develop numerous pharmaceuticals, including tissue plasminogen activator (t-PA), which can prevent damage from heart attacks; erythropoietin (EPO), which stimulates red blood cell production for AIDS and kidney dialysis patients; colony stimulating factor, which stimulates white blood cells; and factor VIII, for other blood deficiencies. Co-transformation's generated nearly 30 licenses to commercial enterprises. (Odza, 21stC, Vol. 3, Issue 1)

Bayh-Dole enables the technology transfer of intellectual property rights emanating from U.S. government research grants to U.S. academia. Today, research grants to universities amount to about $30 billion annually. These grants have made U.S. research universities and medical centers the R&D pipeline for the U.S. biotechnology industry. Without Bayh-Dole, the biotechnology industry as we know it today might not exist.

Diamond v. Chakrabarty, 1980

Reliable, consistent and enforceable intellectual property protection for patents, trademarks, trade secrets, etc. has been fundamental to US commerce. The US Constitution enables Congress to pass intellectual property protection laws. Title *35 U. S. C. § 101* provides for the issuance of a patent to a person who invents or discovers "any" new and useful "manufacture" or "composition of matter." Historically, Congress and not the courts, must define the limits of what can and cannot be patented. Once Congress has spoken, it is "the province and duty of the judicial department to say what the law is." (Marbury v. Madison, 1803). Congress has performed its constitutional role in determining patentable subject matter in § 101 and the federal judiciary has defined and enforced the language of Title *35 U. S. C. § 101.*

In 1977 the first practical application of genetic engineering occurred with the production of human growth hormone by genetically engineered bacteria. In 1978, Genentech Inc. produced human insulin in genetically engineered *E. coli*. The biotechnology industry is launched. However prior to 1980, one key question remained unanswered. Could genetically engineered organisms be patented? Patent protection would be essential to make genetic engineering commercially viable for Genentech and future biotechnology companies.

Patents are the most reliable and strongest form of intellectual property protection. No other industry is more sensitive to the protection afforded by strong patents than the biotechnology industry. The ability to gain commercial protection for the results of R&D determines the value of a biotechnology company and is the basis for attracting investments. The biotechnology industry starts with risk equity investments and is sustain by the continued ability to raise capital through equity sales. Without sound patent protection to provide assurances to the equity investor, biotechnology does not get started and is not sustained. (Bradford, *Export Your Innovations and Unlock Shareholder Value*)

The answer to the question of the patentability of genetically engineered organisms came in 1980 with the US Supreme Court's decision in Diamond v. Chakrabarty. The Supreme Court affirmed the judgment of the Court of Customs and Patent Appeals that allowed the issuing of a patent for a genetically engineered organism. The Supreme Court upheld that the language of Title *35 U. S. C. § 101* covered the invention of a living, genetically engineered microorganism.

Diamond v. Chakrabarty concerns the patent rights to a genetically engineered microorganism that breaks down crude oil. Mr. Chakrabarty, a microbiologist, sought to patent his artificially made bacterium under Title 35, U.S. Code 101. The patent was to be assigned to the General Electric Co. Title 35 authorizes the patenting of any newly made manufacture of composition of matter. The original patent examiner denied Mr. Chakrabarty's patent claim on the grounds that Title 35 did not allow for such a patent. The Patent Office Board of Appeals agreed with the examiner. The ruling was appealed to the Court of Customs and Patent Appeals which overturned the ruling of the Patent Office Board of Appeals in favor of Mr. Chakrabarty. The US Patent Office seeking to deny the issuance of the patent to Mr. Chakrabarty then appealed this ruling to the US Supreme Court. The US Patent Office asked the Supreme Court to determine whether a live, human-made micro organism is patentable subject matter under *35 U. S. C. § 101*.

Chief Justice Burger wrote the majority opinion which ruled in favor of granting the Chakrabarty patent. The decision was split five to four among the Justices. In his opinion, Justices Burger states that when the patent laws were recodified in 1952, Congress replaced the word "art" with "process," but otherwise left Thomas Jefferson's language intact. Congressional committee reports accompanying the 1952 Act clearly indicate that Congress intended that patentable subject matter to "include anything under the sun that is made by man." The Chief Justice went on to acknowledge in his opinion the economic relevance to the patent process. He wrote," Whether respondent's claims are patentable may determine whether research efforts are accelerated by the hope of reward or slowed by want of incentives, but that is all." (*Diamond v. Chakrabarty*, 447 U.S. 303)

The legal community has always considered the Diamond v. Chakrabarty ruling as narrow in focus. However, the biotechnology industry saw the 1980

ruling as the protection necessary to embark on the investment of billions of dollars that has taken us from the characterization of the DNA double helix to Dolly the sheep and to the development of scores of biotherapeutic drugs and diagnostics. Without Diamond v. Chakrabarty, commercial biotechnology based on recombinant DNA technologies would not exist today.

Conclusion

The forces leading to the emergence of the biotechnology industry in the U. S. are as complex as the science of biotechnology. There were fundamental elements that needed to be in place for the industry to emerge. First, the science of biotechnology must available to be translated into new and commercially high value products. Next, large amounts of high risk capital must be available to finance the interpretation of biotechnology science into high value products. Finally, the science and the products derived from biotechnology must have strong intellectual property protection.

The convergence of three actions taken by the U.S. government in 1980 provided the platform to launch the biotechnology industry in its current form. The Bayh-Dole Act provided a robust pipeline of university research and scientific discovery in the form of licensed intellectual property that could and continues to be translated into start-up biotechnology companies. The "feed stock" for high risk venture capital investments in start-up biotechnology companies comes directly from the enactment of Bayh-Dole.

Venture capital investments in biotechnology require the certainty of strong intellectual property protection for the science and the products derived from the science. The Cohen-Boyer patent and the Chakrabarty ruling demonstrated to the venture capital world that the requisite strong intellectual property protection could be secured in the U.S.

Many factors such as economic cycles, government regulations, medical needs and third party insurer reimbursements have contributed to the emergence, growth and maturation of the biotechnology industry. But the convergence in 1980 of Cohen-Boyer, Bayh-Dole and Chakrabarty enabled venture capital investments to be made, companies to be formed and products to be introduced to the market place. This convergence was essential to launch the biotechnology industry and it happened in 1980.

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Title *35 U. S. C. § 101*.

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