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Commercializing Cohen-Boyer 1980-1997

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Abstract:

This paper examines the history of the licensing and subsequent commercialization of the Cohen-Boyer Patents. These licenses are considered among the most successful examples of university technology transfer in terms of generating revenue and creating a range of new products. Stanford was negotiating new ground with their licensing program and they consulted widely in the design and implementation their program. The paper begins by providing the context for Stanford's approach to licensing and then examines the implementation of the licensing practices and procedures. The final section of the paper examines the commercial products that companies developed using the technology and the resulting licensing revenues. We demonstrate that even with a successful nonexclusive license the outcome is highly skewed with about 80% of the revenues originating from ten companies with a small number of products.

Key words: Cohen-Boyer, patents, university technology transfer, licenses, biotechnology

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On December 2, 1980, Stanford University was granted a patent for recombinant DNA methods developed by Drs. Stanley Cohen, of Stanford University; and Herbert Boyer, of the University of California in San Francisco. Entitled *Process for Producing Biologically Functional Chimeras*, this patent provided the basis for among the most successful university technology licenses both in terms of generating revenue and creating a range of new products. The Cohen-Boyer licenses heralded a new era of university-industry relationships and set a standard for subsequent efforts to commercialize academic discoveries. Many universities attempt to emulate Stanford University's success at technology transfer; however, there is a limited appreciation of the creativity and adaptability of the Office of Technology and Licensing (OTL) in setting up their licensing program and the myriad of decisions that guided the ultimate outcome. In spite of many obstacles, Stanford University pursued the recombinant DNA patents and designed a strategy that licensed the technology to 468 companies, many of whom successfully commercialized derivative products.

Numerous authors have examined Cohen and Boyer's scientific discovery, the decision to patent, and the controversies surrounding the use of recombinant DNA from a myriad of perspectives.¹ Less is known, however, about the subsequent development of this technology: the tangible details of how Stanford University licensed what is now recognized as the first research tool, together with the economic impact that the Cohen-Boyer licensees had on the emergence and development of biotechnology. Our objective is to examine the history of the commercialization of the Cohen-Boyer technology, focusing on the issues that Stanford University faced over the life of the patents and the problems they encountered licensing this powerful new technology. Specifically, we consider the evolution of the licensing agreements, presenting an overview of the companies that licensed the technology, the products they commercialized, and the overall economic impact of the patents.

It is important to keep in mind that Stanford University had four goals which guided the development of the Cohen-Boyer license: to be consistent with the public

¹ For an earlier history of Cohen-Boyer, focusing on the story of discovery and decision to patent, see: Sally S. Hughes, 'Making Dollars out of DNA. The First Major Patent in Biotechnology and the Commercialization of Molecular Biology, 1974-1980', *Isis*, 92, (2001), 541-75.

service ideals of the university; to provide the appropriate incentives in order that genetic engineering technology could be commercialized for public use and benefit in an adequate and timely manner; to manage the technology in order to minimize the potential for biohazard; and lastly, to provide income for educational and research purposes.² While these were certainly noble goals, at the onset no one was sure how to go about establishing and enforcing a licensing strategy that would satisfy them. In fact, it was not even clear at the outset whether the university could, or even should patent the method and related tools.

Recombinant DNA: Can You Patent a Breakthrough Technique?

In what was to become a characteristic pattern of consulting widely, Robert Rosenzweig, Vice President for Public Affairs at Stanford, sought to build consensus by asking the faculty to comment on whether the university should proceed with the patent process. In a 1976 letter addressed to “Those Interested in Recombinant DNA,” Rosenzweig wrote, “While I do not believe that personal profit is a base or ignoble motive, it happens that no member of the Stanford faculty stands to be enriched personally as a result of this patent.”³ He thus separated the idea of personal scientists’ profit from the intellectual property issue by dispelling the notion, displeasing to many scientists, that Cohen and Boyer would accept royalties from any prospective patent.⁴

However, the university *did* stand to be enriched by the patent royalties, and the prospect was perhaps not so unwelcome at the time when federal funding for academic research was declining. Rosenzweig continued: “It is a fact that the financing of private universities is more difficult now than at any time in recent memory and that the most

² Kathy Ku, ‘Licensing DNA Cloning Technology’ paper presented at the LES USA/Canada Central/Western Regional Meeting, Scottsdale AZ, February 1983, page 115. A copy was obtained from the Stanford University OTL, 17 August 2004.

³ Letter from Robert Rosenzweig to ‘Those Interested in Recombinant DNA,’ dated June 4, 1976. Obtained from: United States. Office of the Director, N. I. H. (1978). Recombinant DNA Research: Documents Relating to ‘NIH Guidelines for Molecules,’ June 1976 to November 1977. In: U.S. Department of Health, and Welfare (ed.).

⁴ According to Hughes’s chronicle, Cohen immediately renounced any personal share of the royalties generated by any potential patent. At that moment, Boyer was not so eager to renounce his share of the royalties, but he did do so later on, circa 1974. Cohen later reclaimed his share of the royalties, noting that he wanted to take more control over the use of the funds. It is noteworthy to mention that both inventors were in an interesting position with regards to industry at this point. Cohen was a scientific advisor to Cetus Corporation, which ultimately pursued a license on the technology, and may have served on other boards as well. For his part, Boyer had just founded Genentech with Robert Swanson, in April 1976.

likely prediction for the future is that a hard struggle will be required to maintain their quality.” As a result of these financial concerns, he concluded: “...we cannot lightly discard the possibility of significant income that is derived from activity that is legal, ethical, and not destructive of the values of the institution.”⁵ The prevailing standard at the time was that scientists did not patent scientific techniques, regardless of commercial potential. So-called “product” patents were acceptable—even Cohen had previously patented a filter model that he had invented—but “process” patents, ones that claimed general techniques, were less well-known.⁶ That Cohen had to be heavily persuaded by the director of the Office of Technology Licensing, Neils Reimers, to file an invention disclosure is testament to the newness of the concept of university patents.⁷

Much of the academic reticence to patent stemmed from the prevailing norms that pure university science and commercial industry should not mix; that the pursuit of scientific truth should not be confused or tarnished by any motives of personal profit. As Donald Fredrickson, then the NIH director, put it:

No matter where one was positioned in the early part of the recombinant DNA era, ‘the patent’ was widely perceived as a modestly seismic event, a nervous shift at the conjunction of the academic/not-for-profit and commercial tectonic plates sustaining the crust of the biomedical research enterprise. To some scientists of my generation and fairly cloistered experience at NIH, it also heralded a certain loss of innocence.⁸

Of course, there was precedent for university patenting, which has been documented elsewhere.⁹ At the time, patent rights from federally funded research were automatically awarded to the sponsoring agency; however, academic institutions could petition the sponsoring agency to assign the patent rights to the inventors’ institution under a specially negotiated Institutional Patent Agreement (IPA).¹⁰ In 90% of the cases, the institutions were granted the patent rights and were thus able to move the inventions

⁵ Robert Rosenzweig, 1976, OTL archives.

⁶ U.S. Patent 3730352, filed December 6, 1971, and issued May 1, 1973.

⁷ Niels Reimers, ‘Tiger by the Tail’, *Chemtech* 17(8), (1987), 464-471.

⁸ Donald S. Fredrickson, *The recombinant DNA controversy: a memoir: science, politics, and the public interest 1974-1981* (Washington, D.C. ASM Press, 2001), 93.

⁹ David Mowery, *Ivory Tower and Industrial Innovation: University-Industry Technology Transfer before and after the Bayh-Dole Act in the United States* (Stanford: Stanford Business Books, 2004).

¹⁰ J.A. Dobkin, ‘Patent Policy in Government Research and Development Contracts’, *Va. L.Rev.* 53, (1967), 564.

to the marketplace.¹¹ Stanford's OTL, one of 16 similar OTL operations at the time, was starting to pursue patents and receive licensing revenues. However, this was the first time that a university pursued a patent on such a widely applicable, paradigm-shifting technique.

On June 18, 1976, Rosenzweig sent a letter to Donald Fredrickson, NIH director, asking his opinion on the patenting of the Cohen-Boyer discovery and enclosed a copy of the previously referenced Stanford memorandum. Fredrickson responded by sending a mass mailing to "a broad range of individuals and institutions," asking them for their comments on the patent question.¹² Fredrickson's letter laid out five possible alternatives that NIH could take regarding recombinant DNA patenting:

Option 1: Institutions could be discouraged from filing patent applications on inventions arising from recombinant DNA research.

Option 2: Institutions could be asked to file patent applications on inventions arising from recombinant DNA research and to dedicate all issued patents to the public.

Option 3: Institutions could be asked to assign all inventions made in performance of recombinant DNA research to the department. The department as assignee of the invention could either pursue the licensing of whatever patent applications were filed or dedicate issued patents to the public.

Option 4: The department could continue to permit institutions to exercise their first option to ownership under the IPA but require that all licensing of patented inventions be approved by the department. The department could set certain conditions for approval, such as compliance with the *NIH Guidelines for Recombinant DNA Research*.

Option 5: The government could permit institutions to retain their first option, as in option 4, but approve only exclusive licenses.¹³

Fredrickson received approximately fifty letters, and the responses reflected the unprecedented nature of the question, as well as the controversy surrounding it. One letter went so far as to assert that recombinant DNA was "common knowledge," because "the idea of recombinant DNA dates back many years before the 1973 and 1974 experiments

¹¹ Donald S. Fredrickson, *The recombinant DNA controversy: a memoir: science, politics, and the public interest 1974-1981* (Washington, D.C. ASM Press 2001), 311: "...waivers were granted in about 90% of the cases, provided the institution showed the ability to move the invention to the marketplace."

¹² United States. Office of the Director, N. I. H. (1978). *Recombinant DNA Research: Documents Relating to "NIH Guidelines for Molecules,"* June 1976 to November 1977. In: E. Department of Health, and Welfare (ed.): Department of Health, Education, and Welfare (hereafter, DHEW), letter from Donald S. Fredrickson to Robert Rosenzweig, 2 March 1978.

¹³ Donald S. Fredrickson, *The recombinant DNA controversy: a memoir: science, politics, and the public interest 1974-1981* (Washington, D.C. ASM Press, 2001), 97.

of Cohen and Boyer.”¹⁴ The author of this letter went on to claim prior art for experiments that he had in fact never performed. Another letter requested ‘... controls so that no scientist will be able to move into...a never-never land where negative results for all of society might come forth.’¹⁵ Another letter from Robert Sinsheimer, then the chairman of the California Institute of Technology Biology department, claimed that the prospect of patenting recombinant DNA was “vaguely ludicrous.” Given that science builds upon previous discoveries, Sinsheimer felt “...it is evident that [Cohen and Boyer’s] contributions here are a small increment to the great advances in our knowledge of molecular biology and molecular genetics over the past 25 years.”¹⁶ One must wonder if the inventors were begrudged their due scientific credit as a punishment for venturing into the commercial realm. Congressmen weighed in as well: John LaFalce wrote on behalf of a constituent, citing the constituent’s belief that, “since all of the information has been derived through grants from the Public Health Service, it is public information and not patentable.”¹⁷

What is interesting is that the vast majority of responses, from industry and academia alike, absolutely opposed an exclusive license of the patents. Option four, which permitted universities to patent recombinant DNA research but still required NIH approval of all licensing practices, received the greatest support. “Especially in this field,” wrote Dr. Green, “which is susceptible to such a wide variety of applications, exclusive licensing of a basic patent might well be unwise and unnecessary. One company cannot explore all possible applications which might be dominated by a basic patent.”¹⁸ Even some companies that would surely have benefited from having exclusive rights to recombinant DNA oppose that measure. Cetus Corporation, for example, where Cohen was a scientific consultant, wrote to Fredrickson that, “... any *exclusive* license, granted to anyone... would be extremely unwise.” Later in the letter, they explain:

¹⁴ Letter from Garret M. Ihler, M.D. Ph.D., Associate Professor of Biochemistry, University of Pittsburgh, to Donald Fredrickson, 30 June 1976. DHEW, 2, 62-63.

¹⁵ Letter from Esther Peterson, Vice President for Consumer Programs for Giant Food, Inc., to Donald Fredrickson, dated October 5, 1976. Obtained from Recombinant DNA Research, Volume 2; Page 136-137. DHEW.

¹⁶ Letter from Robert L. Sinsheimer, Chairman of California Institute of Technology Division of Biology, 14 September 1976. DHEW, 74,

¹⁷ Letter from Congressman John LaFalce to Donald Fredrickson, 9 August 1976. DHEW, 68.

¹⁸ Letter from Harry Green, Ph.D. Director, Scientific Liason of Smith Kline & French Laboratories, 17 September 1976. DHEW, 78.

In the past exclusive licenses may have been seen as the only way to motivate industry to make the necessary investment commercially. This is clearly not the case here. Many companies have already asserted their intention to become involved in the field – it is difficult to understand how any significant biologically-based company could do otherwise.¹⁹

This was a strong stance for the “young Bay Area company”²⁰ to take, especially given the fact that at this point it was uncertain whether they could survive without exclusive rights to the Cohen-Boyer patent. Yet another company Genentech, founded by Robert Swanson and Herbert Boyer in April 1976, had already requested a worldwide exclusive license from Stanford, insisting that those rights were “critical to [their] survival.”²¹ As Niels Reimers put it, if the university decided to issue only nonexclusive licenses, “Genentech will not obtain its desired exclusive [...] it may mean that Genentech as a viable company cannot survive.”²² One could argue that the corporate push for a nonexclusive license stemmed from a fear that *someone* (probably Genentech, given the company’s connections) would obtain the exclusive license and exclude all others from the recombinant DNA business. However, in hindsight given the extraordinary success of the patents and the sheer number of products that the technology spawned, it seems clear that non-exclusive licensing was the appropriate choice.

While economic logic dictates that non-exclusive licensing of a fundamental process patent would be the socially optimal method, it is important to note that Stanford’s actions are not attributable to economic logic. Nor did Stanford follow the recommendation of the Bayh-Dole Act that passed December 12, 1980 which favored exclusive licensing to a small company.²³ The policy that Stanford ultimately created was a true compromise between those in academia, who opposed any academic commercialization of intellectual property, and those in industry, who saw any special

¹⁹ Letter from Ronald E. Cape, Ph.D, President of Cetus Corporation, to Donald Fredrickson, 28 September 1976. DHEW, 94-97.

²⁰ Sally S. Hughes, ‘Making Dollars out of DNA. The First Major Patent in Biotechnology and the Commercialization of Molecular Biology, 1974-1980’, *Isis* 92(3), (2001), 564.

²¹ Letter from Ronald E. Cape, Ph.D, President of Cetus Corporation, to Donald Fredrickson, 28 September 1976. DHEW, 94-97,

²² *Ibid.*, 94-97.

²³ The Bayh-Dole Act is the 1980 enactment of P.L. 96-517, The Patent and Trademark Law Amendments Act.

treatment of recombinant DNA as unnecessary government meddling. Upon reflection, Fredrickson wrote:

I'm constrained to think what would have happened if the congressmen who abhorred the patenting of federally sponsored inventions had worked their will. I am certain we were right to cover technical inventions that would push the art as far as it has gone.²⁴

Two controversies were involved in the recombinant DNA debate over Stanford's ability to patent. The first was whether a university could or should be able to patent anything that resulted from research funded by federal dollars. As this predated the passage of the Bayh-Dole Act, there was significant debate around this issue. The second was whether recombinant DNA was too dangerous to continue research on—many feared a man-made biological chimera could create a public health catastrophe. Both of these issues are present in the responses to Fredrickson's letter, and both shaped Stanford's eventual licensing policies. The university ultimately honored the consensus opinion that the technology be offered under a nonexclusive license.

The Patent in Waiting

Despite the controversy, Stanford continued to press forward. Although the original 1974 patent application had claimed both the process of making recombinant DNA and any products that resulted from using that method, the USPTO had denied the product claims. Stanford then divided the claims into two divisional product applications, one that claimed recombinant DNA products produced in prokaryotic cells²⁵ and the other claimed the same but in eukaryotic cells.²⁶ Because of the divisional applications, Stanford had to file a terminal disclaimer, which meant that all subsequent application claiming recombinant DNA, regardless of how long the patent prosecution process took, would expire on December 2, 1997—the same date as the original 1980 patent.²⁷ In effect, Stanford agreed to give up royalty rights on the life of the subsequent patents (issued in 1984 and 1988) that would have extended past the original patent's expiration

²⁴ Donald S. Fredrickson, *The recombinant DNA controversy: a memoir: science, politics, and the public interest 1974-1981* (Washington, D.C. ASM Press, 2001), 93.

²⁵ A prokaryotic cell is one without a contained nucleus.

²⁶ A eukaryotic cell has a contained nucleus.

²⁷ "The Patent Office often requires terminal disclaimers to prevent an applicant seeking to extend patent life from filing continuation applications", see Niels Reimers, 'Tiger by the Tail', *Chemtech* 17(8), (1987), 469.

date. This had the potential to limit Stanford's collection of royalties because of the time delay inherent in the commercialization of potential products, especially pharmaceutical products. Thus Stanford was motivated to license as quickly as possible.²⁸

(Figure 1 about here)

In an unusual move, Stanford's opened the patent prosecution file to the public. Applicants generally keep patent applications secret from the date they were filed until they were granted. Stanford had kept the prosecution process open during the filing of their first two patents (the recombinant DNA method and the prokaryotic product patents), "to strengthen [their] position if someone later went after [them] for USPTO fraud."²⁹ Stanford had taken this step because, as he stated:

challenges to the patents in the courts seemed certain... Anyone who was aware of factors which would affect the patent's validity was asked to make them known to the Patent Office... Any company seeking to challenge the validity of the patent after its issue would then have the burden of justifying why they had not raised those issues with the Patent Office before the patent issued.³⁰

This was absolutely consistent with Stanford's earlier stated goal to keep the university's motives and developments transparent.³¹ Their strategy was similar to those patent-holders who seek re-examination on their own patents, or file an opposition to them. The

²⁸ "Bert Rowland called one day to suggest that Stanford should look into extending the patent via a patent extension act. He argues that Stanford could make the case that Stanford did not receive its fair share of royalties since so many products were delayed in the FDA. We asked him to look into the situation and give us more information on the exact procedures to obtain the extension and the chances it could be extended. When we found out that it took an act of Congress and the signature of the President of the United States we felt that the chances of an extension would be remote. In addition, and almost more importantly we felt we had an obligation to our licensees, since we told them (and acted accordingly) that the terms on the patent was until Dec. 3, 1997 because of terminal disclosures. We were definitely not prepared to defend against the anticipated outrage that the biotech community would have if they would be required to pay royalties for a longer time....The idea resurfaced one more time in later years but we again decided that it would not be good public policy or public relations if we were to ask for or even get such an extension." Kathy Ku personal notes.

²⁹ Personal communication, Niels Reimers to Kathy Ku, 28 March 2002.

³⁰ Niels Reimers, 'Tiger by the Tail', *Chemtech* 17(8), (1987), 464-471.

³¹ "It is essential that the University be open about the entire process. We should not try to hide our actions or disguise our motives", see United States. Office of the Director, N. I. H. (1978). Recombinant DNA Research: Documents Relating to "NIH Guidelines for Molecules," June 1976 to November 1977. In: E. Department of Health, and Welfare (ed.): Department of Health, Education, and Welfare.

logic in this strategy is that it sharply reduces subsequent questioning about the patent's validity.³²

This debate was contained within the U.S., because Stanford had been unable to file a patent that would be valid internationally. U.S. patents have a one year grace period between publication of discovery and application date; international patents require application before publication. Because of their 1973 publication, Cohen and Boyer were precluded from filing for an international patent. Indeed, they were nearly precluded from filing even a U.S. patent—they made the cutoff date by only one week.³³ As Stanford intellectual property was not protected worldwide, Cohen and Boyer had to prepare for a potential problem with companies using the technology to make products overseas and then selling them in the U.S. market. To prevent this, Stanford used Section 337 of the Tariff Act of 1930, which prohibits unfair foreign trade. The Act was intended to protect U.S. manufacturers from unfair competition, and the remedy was either trade exclusion or a cease and desist order. At the time when concerns about American competitiveness were paramount, this was a credible threat. Tom Kiley, a lawyer at Genentech, noted that Stanford's message in negotiating with the Japanese was: "Take a license or get your socks sued off."³⁴

All these factors shaped the licensing terms and strategy that Stanford ultimately pursued. Anticipating the obstacles the OTL was about to face, Kathy Ku later noted, "Stanford was trying to license an invention for which products had never been sold and which would apply to many diverse, established industries, in addition to the newly emerging biotechnology industry."³⁵ The novelty of their endeavor presented an opportunity for creativity that would serve as a reference point for the future practices of university technology transfer.

³² Bronwyn H. Hall, Stuart J.H. Graham and Dietmar Harhoff, 'Prospects for improving patent application via post-grant opposition', *National Bureau of Economic Research Working Paper*, (2003), Available at: <http://www.nber.org/papers/9731>.

³³ An earlier publication in the *New Scientist* will surface later in this story, becoming another impediment to the issuance of this patent.

³⁴ Kathy Ku, 'Licensing DNA Cloning Technology', paper presented at the LES USA/Canada Central/Western Regional Meeting, Scottsdale, AZ, February 1983, page 115. A copy was obtained from the Stanford University OTL, August 17, 2004.

³⁵ *Ibid.*, 114.

License First, Ask Questions Later: Patenting Was the Easy First Step

Niels Reimers was up to the challenge and he was not about to give up just because this type of licensing had not been done before. After all, the entire project was largely fueled by his insistence that Cohen file the original invention disclosure.³⁶ He had founded Stanford's OTL and later assumed the role of director after noticing that the existing university patent procedure was not particularly lucrative or efficient.³⁷ Reimers continued to insist that the OTL press forward with the licensing process, even while the scientific community debated the legitimacy of a university patent and the potential biohazards caused by recombinant DNA. In a memo dated July 11, 1976, Reimers wrote: "At the onset, we must acknowledge that we are going to have to act on imperfect information. Ten months or 10 years from now we'll know what we should have done."³⁸

There were three encumbrances that became apparent while the OTL was drafting the licensing terms. Since the publication of the research article in 1973, many companies had already started using recombinant DNA. From a technical standpoint, it was inexpensive and easy to use, especially when compared to the previous experimental methods of splicing together bits of DNA. Recombinant DNA was a panacea of sorts, with vast applicability spanning a range of industries including agriculture chemicals, pharmaceuticals, and food products. William N. Hubbard, then President of the Upjohn Company, noted that entrepreneurial start-ups such as Cetus Corporation, Genentech, Genex and Biogen had active commercial development programs in recombinant DNA.³⁹ In fact, Genentech's first recombinant DNA product, a small hormone called

³⁶ Niels Reimers recalled that "he had to talk to Cohen 'like a Dutch uncle' " in obtaining his permission to file a patent application." Sally S. Hughes, 'Making dollars out of DNA. The first major patent in biotechnology and the commercialization of molecular biology, 1974-1980', *Isis* 92(3), (2001), 549.

³⁷ Niels Reimers, and Sally S. Hughes, Bancroft Library. Regional Oral History Office. & Program in the History of the Biological Sciences and Biotechnology. (1998). *Stanford's Office of Technology Licensing and the Cohen/Boyer cloning patents*. Berkeley, Calif.: Regional Oral History Office The Bancroft Library University of California. Online Archive of California; <http://ark.cdlib.org/ark:/13030/kt4b69n6sc>

³⁸ This quote is taken from Kathy Ku's, "Licensing DNA Cloning Technology" paper presented at the LES USA/Canada Central/Western Regional Meeting, Scottsdale AZ, February 1983, page 15. A copy was obtained from the Stanford University OTL, August 17, 2004.

³⁹ William N. Hubbard Jr., 'The Industrial Potential of Recombinant DNA Technology', *Vital Speeches of the Day*, 46 (11), (1980), 342 – 348.

somatostatin, was initially produced in 1977.⁴⁰ Large pharmaceutical companies such as Hoffman-La Roche, Merck, Imperial Chemical Industries, G. D. Searle, Eli Lilly, and Upjohn and other firms such as General Electric were also using the Cohen-Boyer method.⁴¹ Thus, the OTL had to invent a non-oppressive licensing strategy that would encourage cooperation, because it was also becoming clear that infringers of a process patent would be much more difficult to hold accountable. There was no clear way to know if a company was using the technology. The evidence required to prove that a company was infringing would have to come from their own company records or the testimony of a current or former employee and most likely would be part of legal discovery that would accompany litigation.

An additional problem was the lack of precedent for non-exclusive licenses and specific licensing terms. As applicable as the technology was, the licensing strategy also had to accommodate many players of different types, and Stanford accomplished this by continuing to consult widely. As Kathy Ku explained,

Discussions with several companies of differing sizes and markets were held while the license terms, particularly earned license terms, were being formulated. By doing this, the license was 'presold' and unrealistic licensing terms were avoided.⁴²

To make this process easier, the OTL took great pains to categorize the different potential recombinant DNA products and to offer appropriate royalty rates. By Reimers' account, this was aided by the consultation with Lou Wolk, the then-retired chief patent counsel at Merck. The OTL obtained permission from Merck to hire Wolk as a temporary consultant while discussing royalty structures, and he and Reimers had two telephone conversations regarding the relationship of bulk products and end products.⁴³ In the end, the OTL settled on four different product categories: basic genetic products, bulk products, end products, and process improvement products. By scaling the rates to reflect

⁴⁰ Sally S. Hughes, 'Making Dollars out of DNA. The First Major Patent in Biotechnology and the Commercialization of Molecular Biology, 1974-1980', *Isis*, 92(3), (2001), 566.

⁴¹ William N. Hubbard Jr., 'The Industrial Potential of Recombinant DNA Technology', *Vital Speeches of the Day*, 46 (11), (1980), 342-348.

⁴² Kathy Ku, 'Licensing DNA Cloning Technology' paper presented at the LES USA/Canada Central/Western Regional Meeting, Scottsdale AZ, February 1983. A copy was obtained from the Stanford University OTL, 17 August 2004.

⁴³ Personal communication, Niels Reimers to Alessandra Colaianni, 27 July 2005.

the visibility of the licensee's product and the expected revenue from each license, the OTL encouraged compliance. A graduated royalty system also avoided penalizing the smaller companies with low sales volume.

(Figure 2: Charts here with different product types)

Under the licensing agreements, Stanford received royalties on the drug's sales in an unprecedented way, later known as reach-through licensing.⁴⁴ In a reach-through license, the licensor receives royalties on end product based on a percentage of final sales, even when the licensed technology is not incorporated into the final product. Licenses with reach-through royalty provisions solve the problem of placing a value on a research tool before knowing the outcome of downstream product development.⁴⁵ Under the Cohen-Boyer patent, firms accepted a reach-through royalty obligation because the patent claims extend to all products developed using that technology. Most simply, without authorized use of the recombinant DNA technology, no end products could be produced without infringement of the Cohen-Boyer patent.

In order to deal effectively with the business world, Stanford OTL had to act more like a business. As a non-profit entity, Stanford's OTL was unfamiliar with well-established routines of business practice. While the OTL had been active since its inception in 1969, licensing technology of this magnitude was more complex than anything it had seen before. This difficult transition was perhaps best exemplified by the trouble the OTL encountered while trying to collect the first set of annual payments, as of the February 1, 1981 deadline none of the licensees had paid their dues. There was a possible but not encouraging explanation: the legitimacy of the patents had been recently challenged at a Cold Spring Harbor Laboratory meeting, by a lawyer who would become quite a thorn in the OTL's side—Albert Halluin. However, despite the negative publicity that Halluin's comments had raised, Stanford was still actively pursuing the continuation applications it had filed on the product patents. Due to this challenge Stanford feared that

⁴⁴ Thomas J. Kowalski and Christian M. Smolizza, 'Reach-through Licensing: A US Perspective', *Journal of Commercial Biotechnology*, 6(4), (2000), 349-357.

⁴⁵ Rebecca S. Eisenberg, 'Technology Transfer and the Genome Project: Problems with Patenting Research Tools', *Risk: Health, Safety, and Environment*, 5, (1994), 163-174.

companies might be withholding payment as a protest or because they were considering terminating their agreements. Kathy Ku, then a licensing associate, was given the job of finding out why the companies had not paid. The facts turned out to be far less ominous than Stanford feared. In calls to the licensees, Ku discovered that the companies had not sent in payment because they were waiting for invoices – a standard business procedure, but something completely foreign to the standard operation procedures of a research university.⁴⁶

⁴⁶ Kathy Ku personal notes.

The Devil in the Details: Defining Licensing Terms and Practice

As early as 1975, Niels Reimers recognized that the Stanford OTL had to start planning for the possible licensing of the technology.⁴⁷ In keeping with their strategy to consult broadly, he hired William O'Neill (a business consultant whose specialty was biochemistry), Andy Barnes (a newly minted Stanford MBA whose work was in developing marketing tools and implementing the licensing program) and Lou Wolk (who, as previously mentioned, had just retired from Merck pharmaceuticals) to help design and implement a licensing strategy. Adrian Arima, a Stanford attorney, assisted the group with the wording of the licensing agreements.⁴⁸ The team members combined complementary experiences and perspectives, and together managed a three criteria marketing strategy. Given that the licenses were to be non-exclusive, the terms had to be broad enough to encompass the many industries that were interested in the technology with licensing terms reasonable for both large companies and start-ups. The second criterion was to offer modest enough fees and royalties that companies would rather take a license than to litigate. Stanford also set up a defensive litigation fund in the likely event that companies decided to challenge the patent.⁴⁹ The third criterion of the marketing strategy was to provide incentives for companies to take a license as soon as the patents were issued, because of the anticipated delay time in developing and commercializing products.

There was also a need to design a credible royalty reporting form, and the OTL:

...decided to make it 'fool proof' so that any accountant could easily take into account the complex royalty structure of credits and decreasing royalties based on annual sales in the US and a fixed royalty for non-US sales. We developed the royalty reporting form with the express intention that it look like an IRS form and that, if one followed the directions, it would be simple to fill out.⁵⁰

⁴⁷ Kathy Ku personal notes.

⁴⁸ Personal communication, Niels Reimers to Alessandra Colaianni, 27 July 2005.

⁴⁹ The litigation reserve fund was set up as \$300,000 from the original proceeds collected in December 1981 and February 1982. Although the OTL recognized that this amount of money would not go far if companies were to initiate litigation they would have been able to deploy the proceeds from licensing should the need arise. Widespread knowledge of this fund may have provided a credible threat of enforcement of the license. Kathy Ku personal notes.

⁵⁰ Kathy Ku personal notes.

To further simplify the royalty-reporting procedure, in January of every year each licensee would receive a letter from Floyd Grolle, Stanford's Manager of Market Research. These letters provided information about the licensing program and remind company representatives about the terms of the license and how to calculate royalties due.

All in all, the first license's terms were a \$10,000 upfront fee with a minimum annual advance (MAA) of \$10,000. Earned royalty rates on products were provided on a graduated basis for 3% on the first \$5 million sales of bulk products to 0.5% on end product sales over \$10 million. For process improvements on existing products, the royalty rate was 10% of the calculated cost savings that resulted from using the technology.⁵¹ The largest incentive for companies to take a license as soon as it was available was a credit towards future royalties over the first five years, up to \$300,000. As explained by Kathy Ku:

It was believed that offering the five times credit for a limited time would encourage companies to take a license sooner rather than later (which could be much later) when products were finally on the market.⁵²

A second incentive was that companies were advised that the licensing terms might change. If a company wanted certainty, they were advised to sign up as soon as possible. To encourage companies to sign up, their contracts had to be received by December 15, 1981, to receive the benefits. "Once the terms were set, Stanford printed the license on blue paper to give the impression that the terms were non-negotiable,"⁵³ and single-spaced the document to leave no room for companies' potential revisions.⁵⁴

⁵¹ The difference lies in the applications of the developed marketable goods having at least one component coming within licensed products, or produced by a licensed product. If the products are intended or marketed for further formulation, processing, or chemical transformation, they are catalogued into Bulk Products and if they are not, they belong to End Products. The basic genetic products refers to those materials which are sold or used primarily for further processing or genetic manipulation and/or are neither End Products, Process Improvement Products or Bulk Products. And the Process Improvement Products means those materials are used in manufacturing processes to enhance production efficiency. Graduated royalty rates are calculated based on the volume of sales for end products and bulk products.

⁵² Kathy Ku, 'Licensing DNA Cloning Technology', paper presented at the LES USA/Canada Central/Western Regional Meeting, Scottsdale AZ, February 1983. A copy was obtained from the Stanford University OTL, August 17, 2004.

⁵³ Kathy Ku personal notes.

⁵⁴ Personal communication, Niels Reimers to Alessandra Colaianni, 27 July 27 2005.

Stanford now had a licensing strategy, a list of interested companies, and a marketing strategy designed to achieve their objectives. The patent issued on December 2, 1980, and as of August 1, 1981, the first of five standard licensing agreements was available. Beginning that day, Stanford advertised extensively.⁵⁵ They placed notices in both *Science* and *Nature* about the licensing agreement, because they “didn't want any company to be able to say ‘we didn't know’ that licenses were being offered.”⁵⁶

Following the Silicon Valley model of an Initial Public Offering (IPO), marketing took the form of a road show that entailed presentations to companies in the U.S., Europe and Japan. A six month sales time was seen as optimum to developing interest and keeping momentum.⁵⁷ Niels Reimers and Andy Barnes prepared an extensive interpretation of licensing terms so that the OTL could provide consistent answers to potential questions. An important purpose in addition to disseminating information was to demonstrate that the terms were reasonable and display that Stanford had thought carefully through its licensing strategy.

No one was certain how many companies might sign up; the OTL staff even had an office betting pool on the number of potential licensees.⁵⁸ The bets ranged from 10 to 20, but at the close of business on December 15, a seemingly remarkable 73 companies had signed up. Stanford publicized the early sign-up numbers to notify stockholders and the public of the company's entrance into the field of biotechnology. After the first annual payments were received in 1982, Stanford had collected \$1.45 million in revenue, which was more than the office's revenue from the prior eight years (see Figure 3).⁵⁹ Stanford's success had begun, but several problems with the patents themselves were soon to surface in a report by Exxon attorney Albert P. Halluin.

Halluin's Hobby

In a 1981 conference on the patenting of life forms (the Banbury Conference), Albert P. Halluin presented a paper entitled ‘Patenting the Results of Genetic Engineering Research: An

⁵⁵ Kathy Ku personal notes

⁵⁶ Personal communication, Niels Reimers to Alessandra Colaianni, 27 July 27 2005.

⁵⁷ Kathy Ku personal notes.

⁵⁸ Ibid.

⁵⁹ The initial sign-up fee of \$10,000 was collected in December 1982.

Overview.’⁶⁰ In it, Halluin called attention to several mistakes that Stanford had made with regards to the patent process. First, Boyer had prematurely disclosed the discovery of recombinant DNA at the Gordon Conference of Nucleic Acids, despite promising Cohen to keep it secret until publication. Dr. Edward Ziff subsequently wrote a brief description of the technique in the *New Scientist*, which came out on October 25, approximately two weeks before Cohen and Boyer’s initial publication.⁶¹ Published a year and one week before the initial patent was filed, the *New Scientist* article could count as a prior publication date and therefore invalidate the original 1974 application and subsequent applications, if a person having ordinary skills in the art (PHOSITA) could use the article to perform the experiment. Halluin cited this article in his paper, calling attention to it that raised a new issue not previously considered by the patent examiner.⁶²

Next, Halluin asserted that at the time the patent application was filed, the vector enabling scientists to produce recombinant DNA was not deposited appropriately at the American Type Culture Collection (ATCC) or publicly available, thus preventing the patent from satisfying the enablement requirement.⁶³ Although the rules covering recombinant DNA deposits were still being formed and there was much debate as to whether a ‘recipe’ for making plasmids would satisfy the requirement, Halluin observed in a footnote that it would be ‘most prudent to make a deposit.’⁶⁴

⁶⁰ David W. Plant, Niels J. Reimers, and Norton D. Zinder, *Patenting of life forms*. (Cold Spring Harbor, N.Y.: Cold Spring Harbor Laboratory, 1982), 67-126.

⁶¹ Edward Ziff, ‘Benefits and hazards of manipulating DNA,’ *New Scientist*, 60(869): 274-275.

⁶² The article was later discarded as evidence of prior publication, because it was not judged to be sufficiently enabling.

⁶³ In 1949, the United States Patent and Trademark Office implemented a requirement that cultures be deposited with patent applications concerning microbiological inventions. The reasoning was that for chemical, electrical, or mechanical patents, a diagram or formula can sufficiently describe the invention, whereas in a microbiological patent, illustrations and narrative descriptions are generally inadequate to define sufficiently the microorganism used and therefore comply with the requirement for a full and complete disclosure of the invention. The Patent Office asked the American Type Culture Collection (ATCC) to serve as depository for patent strains.

⁶⁴ David W. Plant, Niels J. Reimers, and Norton D. Zinder, *Patenting of life forms*. (Cold Spring Harbor, N.Y.: Cold Spring Harbor Laboratory, 1982), 67-126. Halluin wrote, ‘The question whether one must make a deposit of plasmids or vectors or recombinant DNA products has been the subject of debate at that time. One school of thought urges that the written procedures are inadequate may be obtained and even a minor modification may make a rather substantial change in function of the ultimate product. Further, subsequent developments and experiments may prove the original procedure to be inoperative in producing the desired plasmid or organisms. In view of this uncertainty, in an important invention it would be most prudent to make a deposit!’

This was complicated by a scientific mistake in the original patent's description of the plasmid-making procedure. A 1977 article by Cohen, published in the *Journal of Bacteriology*, had revised the procedure by which the plasmids, a key part of the recombinant DNA process, were made.⁶⁵ Without the revisions, the original procedure was incorrect, and would not yield the correct plasmid. This error had not been corrected in the second patent application.

Halluin was dismayed by the errors in Stanford's patent prosecution: 'I couldn't believe it. About everything that I thought that you could do wrong in prosecuting a patent and dealing with the patent office was there.'⁶⁶ In an interview, he explained that he was not targeting Stanford; Cold Spring Harbor and Exxon had been poised to collaborate on a joint biotech venture, and he wanted those scientists 'to have this as kind of a road map about getting patents, because a key part of our collaboration with Cold Spring Harbor was getting inventions and filing patents on the new inventions.'⁶⁷

Regardless of their intent, these were serious charges. To the dismay of the OTL, McGraw-Hill's *Biotechnology Newswatch* was covering the Banbury conference, and the Cohen-Boyer angle sounded interesting. The reporter apparently showed parts of the manuscript to the USPTO in the course of research and due diligence on the story, and as a result, the USPTO withdrew their notice of allowance to Stanford University.⁶⁸ At that point, Stanford had received notice that the patent was set to issue on July 13, 1982, and the OTL expected that 'everything would be smooth sailing.'⁶⁹ Because of the questions Halluin had raised regarding the validity of the patent, the USPTO withdrew their notice of allowance on the basis of four complaints: enablement, product of nature, prior publication, and failure to mention all inventors.⁷⁰ Stanford

⁶⁵ Stanley N. Cohen and Annie C.Y. Chang, 'Revised interpretation of the origin of the pSC101 plasmid', *J Bacteriol* 132(2), (1977): 734-737.

⁶⁶ Interview with Mr. Albert Halluin, July 12, 2005, 4:30 EST. Conducted by Maryann Feldman, Alessandra Colaianni, Joseph Fore, and Robert Cook-Deegan.

⁶⁷ The joint venture between Exxon and Cold Spring Harbor did occur; it was a five-year collaboration. Interview with Mr. Albert Halluin, July 12, 2005, 4:30 EST. Conducted by Maryann Feldman, Alessandra Colaianni, Joseph Fore, and Robert Cook-Deegan.

⁶⁸ The article appears in: *McGraw-Hill's Biotechnology Newswatch*, July 5, 1982 Volume 2, Number 13, Page 1. 'Patent Office Suddenly Withdraws Second Cohen-Boyer Patent.'

⁶⁹ Kathy Ku correspondence with Niels Reimers, dated March 28, 2002.

⁷⁰ First, in January 1975, Niels Reimers sent a letter to Robert Helling and James Morrow, coauthors on the 1973 paper, asking them to disclaim inventorship of recombinant DNA. Helling refused to sign, and in 1982, *Science* reported that he '[did] consider himself a coinventor' of recombinant DNA technology. 'In his opinion, he, Cohen, and Boyer were 'equals' in collaborating on the project. 'I was part and parcel to the whole thing.' (Science, Sun Article) The article noted that Bertram Rowland, the patent attorney prosecuting the case, had tried 'repeatedly' to get Helling to sign a disclaimer or to provide evidence that he was a coinventor, but that Helling had ignored Rowland's inquiries.

was forced to issue a press release disclosing that information. ‘We were devastated,’ Ku remembered. As a direct result of the bad press they were receiving at that time, Stanford reversed their earlier decision to keep the patent prosecution file open, and closed the file to the public; and *Biotechnology Newswatch* covered the story.⁷¹ However, despite these significant questions, and after a bit of difficulty in collecting license revenue, the OTL received a letter in December 1983 from the USPTO saying that the patent’s claims were approved and the patent application would proceed to issue.⁷² Bertram Rowland’s arguments were successful in answering the questions raised in Halluin’s paper, and the rejections made by the USPTO.

But Stanford OTL’s involvement with Halluin was not yet over. He continued to question the validity of the patents when he assumed the job of patent counsel at Cetus. At the time, Cetus was regarded as one of the three most promising biotech companies along with Genentech and Biogen. All three licensed the Cohen-Boyer technology when it first became available and they are regarded as dedicated biotechnology companies given that recombinant DNA was their core emphasis. On February 27, 1984, Halluin sent a letter from Cetus with the annual payment that was due February 1, stating that ‘this payment should not be deemed to be an admission by Cetus of the validity of the patents’ and that ‘Cetus is not currently manufacturing, using or selling any licensed product which falls within the scope of any valid claim.’⁷³ This was a startling challenge that culminated on January 25, 1985 when Halluin sent a letter saying that Cetus would terminate the agreement. The letter claimed that Cetus had three reasons for terminating the license: they were not selling products covered by the patents; the Hatch-Waxman Act provided Cetus with immunity for patent infringement during the FDA pendency; and, Cetus had

⁷¹ The article ‘Patent Office Suddenly Withdraws Second Cohen-Boyer Patent’ appeared in *McGraw-Hill’s Biotechnology Newswatch*, 2(24), (1982), 1.

⁷² Bertram Rowland argued fervently against Helling’s status as an inventor at the behest of Cohen and Boyer, both of whom agreed that he had not been a part of the initial discovery. Rowland also argued that Boyer’s premature disclosure at the Gordon Conference ‘did not constitute public disclosure because the participants at the meeting pledge in advance to hold all discussions in confidence.’ Additionally, Rowland argued that the earlier disclosure was *not* enabling, because ‘important steps in the experiment had not yet been developed,’ and ‘the key plasmid in the experiment was not available.’ (Science, Sun Article)

⁷³ Cetus reasoned that because they were not selling any products for which they had used the Cohen-Boyer method, they did not have to take out a license. This is a strange argument, because they *were* using the methods and compositions of matter covered by the first two patents. In an interview, Halluin said that he was also still questioning the validity of the patents; it is possible that this reasoning stemmed not from any new complaint but from Halluin’s unwillingness to accept the validity of the patents themselves.

questions about the validity of the patent.⁷⁴ On April 25, 1985, the *New Scientist* covered the story:

A leading biotechnology firm has broken ranks with the rest of the industry... Stanford is concerned that the Cetus move may open the floodgates and other companies will either stop paying the annual fee or not sign up...The University must walk a legal tightrope, however. It cannot recklessly accuse Cetus of infringing the patent or the university may end up in court. On the other hand, it does not want to seem to be weak in enforcing the patent.⁷⁵

Cetus' action could potentially put the entire licensing program in jeopardy. Litigation was not an attractive option because Stanley Cohen was a member of Cetus' scientific advisory board. Negotiations between the OTL and Cetus continued through the summer, ending in compromise with a formal letter reinstating the license, signed by both parties on August 22.⁷⁶

Once the Cetus case was settled, Stanford's bargaining power increased. On August 4, 1984, the prokaryotic product patent issued and the standard licensing agreement now covered both the process and the products required for the implementation of the method.⁷⁷ In that same year, sales were brisk for Humulin, the first drug synthesized using the recombinant DNA method, which had received FDA approval in October 1982. This seemed to clear the way for the other products such as Protropin and Intron A, which were under FDA review.

Experimenting with Licensing Terms

Over the process patent's seventeen-year life, the Stanford OTL experimented with five versions of the standard license agreements and three special licensing agreements. In all, a total of 468 companies licensed the Cohen-Boyer technology. This was very much a learning process that balanced the capabilities and willingness to comply of companies, especially in the embryonic biotech industry, with the economic potential of the technology. Success secured by the issue of the two additional product patents and the U.S. Federal Food and Drug Administration (FDA) approval of recombinant DNA products.

⁷⁴ Kathy Ku Personal Communication

⁷⁵ I. Anderson, 'Cetus Launches Biotech Patent War', *New Scientist* 106(1453), (1985): 4.

⁷⁶ Specific details were not publicly released.

⁷⁷ It is important to note that although the Cohen-Boyer patents are referred to as distinct 'process' and 'product' patents, the 'product' claims were not referring to the end products that licensees developed. The 'product' patents claimed compositions of matter (recombinant DNA plasmids) that were then used by companies to make proteins and are a basic component of the production method.

[Table 1 here]

Table 1 summarizes the terms of the five versions of the standard licensing agreement. The first version, which expired on December 15, 1981, offered a credit against future earned royalties as a special incentive. A total of 73 firms signed up under this licensing agreement and 50 of them maintained the license until the patent expired.⁷⁸ The largest share of earned royalties from product sales accrued to these firms.⁷⁹

The second standard licensing agreement, effective January 1, 1982, dropped the royalty credit incentive, with the effect that only fifteen additional companies signed up. However, the relative lack of interest may have been due to the previously mentioned public controversies, dubbed as “Halluin’s Hobby.”⁸⁰ On August 4, 1984, the prokaryotic product patent was issued, and the standard licensing agreement now covered both the process and the products required for the implementation of the method.⁸¹ In that same year, sales were brisk for Humulin; the first drug synthesized using the recombinant DNA method, received FDA approval in October 1982. This cleared the way for the other products such as Protopin and Intron A, which were under FDA review.

On August 1, 1985, the OTL issued its third standard version of the license agreement. This version did not specify earned royalty rates but allowed for negotiation by providing a space to write-in agreed upon rates. The idea was to allow for flexibility in negotiating with different sizes of companies in different product markets. In practice though, the earned royalty rates were almost always at the same graduated rates that were used in the second version (see Table 1). This fact may be attributed to the sharing of information among potential licensees about the prevailing terms and what terms might be expected.⁸² Another ten firms signed up under this licensing agreement.

⁷⁸ The credit was accruable for up to five years, covering products sales until 1987.

⁷⁹ Amgen was grandfathered into this version of the licensing terms.

⁸⁰ I. Anderson, Cetus Launches Biotech Patent War. *New Scientist*, 106(1453), (1985), 4.

⁸¹ It is important to note here that although the Cohen-Boyer patents are referred to as distinct “process” and “product” patents, the “product” claims were not referring to the end products that licensees developed. The “product” patents claimed compositions of matter (recombinant DNA plasmids) that were then used by companies to make proteins and are a basic component of the production method.

⁸² Interview with Kathy Ku, 17 August 2004.

Another adjustment was made on November 1, 1986 with the fourth standard licensing agreement. Instead of a graduated royalty rate, a flat rate of 1% on end products and 3% on bulk products was used. These were the highest rates under the prior license version. For Stanford, this change reflected a realization that the patents could earn higher rates. In response, 21 new firms signed up to license the technology, perhaps motivated by the possibility of further increases in the future.

The fifth version of the Cohen-Boyer standard licensing agreement, adopted in September 1989, demonstrated further strategic changes. The flat earned royalty rates doubled from 1 to 2 % for end products and 3 to 6 % for bulk products, as more were beginning to come to the market. Also, in order to encourage licensing by small start-up companies, consideration of company size was introduced. For companies with less than 125 employees, the sign-up fee and MAA fee remained the same of \$10,000 each. There were also a number of large firms that were just beginning their biotech efforts; for those with more than 125 employees, the sign-up fee and MAA was increased to \$50,000, five times the original amount. The strategy worked—209 small biotech firms became licensees under this version, along with 12 large companies. The rules were not set in stone, however, and the OTL accommodated special cases. For example, Coors Brewery negotiated a small company license because, while they were a large corporation, their biotech program was just beginning and was relatively small.

As discussed earlier, Stanford could not apply for patent protection in Europe or Japan because of the 1973 academic publication. However, by using the International Trade Commission (ITC) to enforce section 337 of the Tariff Act of 1930, Stanford was able to protect itself from companies who would infringe abroad, and sell non-infringing recombinant DNA products in the United States.⁸³ All versions of the licensing agreements provided for royalty rates for foreign sales of 0.5% for end products, 1% for bulk product, 10% for basic genetic products sales and 10% of cost benefits of process improvement. The royalty rates for sales made outside of the United States remained consistent. In retrospect, it seems odd that the foreign licensees agreed to this provision, except perhaps as a means to stake a claim that they were actively involved in the emerging field of biotechnology.

⁸³ Niels Reimers, 'Tiger by the Tail', *Chemtech* 17(8), (1987), 464-471.

In addition to the standard agreements, there were three non-standard licensing agreements issued to accommodate special circumstances in the biotech industry. These are listed in Table 2. The first was an alternative license for small distributors or resellers of recombinant DNA products. While these firms were obligated to pay royalties on products, the sign-up fee and compulsory annual licensing fee of \$10,000 dollars was waived due to a small volume of anticipated sales. In compensation, the royalty rate on end products and bulk products were both doubled to 4 % and 6%, respectively. There were 58 companies who operated under this alternative agreement and total royalties received from this alternative licensing agreement were \$740,070.

At the end of 1994 in consideration of the fact that some startups would not realize product sales within the patent lifetime, a Research and Development license agreement was developed. The sign-up fee was calculated as a one-time payment with the original sign-up fee of \$10,000 waived, and the prorated annual fee due discounted by 20%. A provision was put into effect that if the companies did sell products within the life of the patent, they would have an option to take a regular license. In total, 51 companies signed the Research and Development License agreements, which yielded \$630,069 in total licensing revenues.

The third nonstandard licensing agreement was a final year agreement that offered a sign-up fee and a prorated MAA calibrated to the actual duration from time of sign-up to December 2, 1997.

(Table 3 here)

In total, the Cohen-Boyer licenses generated \$254 million in revenue during its seventeen year term. The initial sign-up and annual fees generated \$26 million, which was ten percent of the total licensing income. A whopping 90% of the total revenue (\$228 million) is from royalty income from product sales. This mirrors the commercial success of recombinant DNA products.

In retrospect, it is evident that Stanford's experimentation with the licensing terms was justified. Encouraging companies to sign up early paid off as that licensing agreement generated approximately 85% of total licensing revenue. This share likely reflects the

time required to bring derivative products to market. The choice to take company size into consideration when negotiating license agreements was prudent and probably further encouraged more licensees to sign up. By 1989, the biotech industry was becoming established and having a Cohen-Boyer license probably helped legitimized these fledgling companies. Uncertainty that the rate might change again encouraged companies not to wait to sign up. Finally, providing three alternative agreements made sure that Stanford could collect as much revenue as possible without being unfair to the special circumstances presented by licensees.

Another special circumstance was the use of the method without licensing of technology by other nonprofit research institutions. This is particularly interesting in light of disturbing developments in research use exemption policies, such as *Duke v Madey* and the WARF stem cell licensing program.⁸⁴ From conversations with Niels Reimers and Kathy Ku, it is evident that the thought of licensing the technology out to other nonprofit research institutions had never entered into anyone's mind. "It was never much of a discussion," wrote Ku.⁸⁵ "There was never a thought of licensing universities," wrote Reimers.⁸⁶ What the OTL *did* recognize and account for in their subsequent licensing programs was the possibility that a research institution would develop a commercially useful transformant (a cell modified by recombinant DNA techniques) that would then be licensed or sold to a company. The OTL would then require any such company to take out a license on the patents.

To understand the impact of this licensing program, we next turn to the commercial products that were introduced to the market.

Commercial Products

Commercial products developed by the licensees generated over \$35 billion dollars in sales of recombinant DNA products over the life of the patent. Stanford reported 2,442 products based on recombinant DNA by the time the Cohen Boyer patent

⁸⁴ The Wisconsin Alumni Research Foundation (WARF) in 2002 signed its first licensing agreement, for stem cells, with an academic provider listed on the NIH registry. This is a big deal, even though WARF is not charging the universities a licensing fee, because it puts WARF in the position of being "at the table" of future inventions using stem cells.

⁸⁵ Personal communication, Kathy Ku to Alessandra Colaianni, 21 July 2005.

⁸⁶ Personal communication, Niels Reimers to Alessandra Colaianni, 21 July 21 2005.

expired in December, 1997, reflecting a range of applications in a variety of industries.⁸⁷ Starting in 1991, there was an average of 400 new products brought to the market every year. Recombinant DNA product sales reached \$500 million dollars in 1987 and then doubled from 1988 to 1990, and doubled again from 1991 to 1994 and yet again from 1994 to 1998. More than 68 % of recombinant DNA products sales were domestic.⁸⁸

Table 4 illustrates the distribution of the Cohen-Boyer licensees by industry. Despite the technology's broad applicability, most of the companies that licensed the Cohen-Boyer technology were from the biotech and pharmaceutical sectors. In fact these two sectors accounted for 96% of the total licensing revenue collected by Stanford. Of the licensees, 68.5% came from the biotech sector, indicating the importance of these patents to the biotech industry. Nearly a quarter of these companies introduced products on the market and paid earned royalties to Stanford. Almost 40% of the pharmaceutical licensees introduced a derivative product.

In total, 468 firms licensed the technology; however, thirteen firms never made any monetary payment to Stanford University. The revenue received from the Cohen-Boyer licensee ranges from \$4.24 to \$54.78 million dollars. Of the 468 licensees of Cohen-Boyer technology, ten companies contributed more than \$197 million dollars (77%) in royalties (Figure 4). Table 5 lists these ten companies.

The next 10 companies accounted for another 10%, while the remaining companies generated less than 13% of total royalty revenue. Many of the products were developed under strategic alliances between start-up biotech firms and large pharmaceutical firms, or between biotech firms. All of the top ten companies, except Merck which signed the agreement in 1984, signed the first standard agreement in December 1980. While others have noted that the distribution of technology transfer revenues are highly skewed, with a few blockbusters accounting for most revenues, our examination of the companies and their products demonstrates that even within a single license, highly skewed outcomes account for the high revenues.⁸⁹

⁸⁷ Compiled from OTL Archives.

⁸⁸ Compiled from OTL Archives.

⁸⁹ Frederic M. Scherer and Dietmar Harhoff, 'Technology Policy for a World of Skew-Distributed Outcomes', *Research Policy*, 29(4-5), (2000), 559-566.

Genentech was the first company to develop therapeutic products based on recombinant DNA technology with products such as human insulin, interferons, human growth hormone, and tissue plasminogen activator. Genentech (GENetic ENgineering TECHnology) was founded in 1976 by Robert Swanson, a partner in the Silicon Valley Venture Capital firm of Kleiner & Perkins. His co-founder was UCSF molecular biologist and recombinant DNA co-inventor Herbert Boyer. In 1978, Genentech scientists successfully cloned human insulin into *E.coli* bacteria and this technology was licensed to Eli Lilly. Humulin, approved by FDA in 1982, was the first commercial recombinant DNA product. Accordingly, Lilly was the first company among the 468 Cohen-Boyer licensees to begin paying earned royalties from its product sales. In 1985, Genentech launched its first commercial recombinant DNA product Protopin, a human growth hormone made by bacteria using recombinant DNA technology. Genentech is also the only company to date to have developed nine blockbuster recombinant DNA products. In 1998, when the patent term had expired, the pharmaceutical products developed by Genentech had annual sales of more than \$4 billion.

Each of these ten companies has a unique story. Further papers might be written that could document the commercialization and market introduction for each of the products developed using recombinant DNA. Indeed, such efforts would inform our understanding of the firm perspective.

Reflections and Conclusions

Now that the patent life for the Cohen-Boyer technology is finished we can begin to evaluate if Stanford University realized the four goals articulated in setting up the licensing program. Certainly, the commercialization of the technology was consistent with the public service ideals of the university. The Stanford Office of Technology Licensing is generally regarded as the most successful in the United States and many other universities seek to provide a similar level of service to faculty and outreach to industry. Assessing the goal of managing the technology in order to minimize the potential for biohazard is beyond the scope of this paper. But it is notable that as the discussion of recombinant DNA evolved from the term genetic engineering to a common use of biotechnology or biotech there has been less public resistance. Certainly the lack

of any serious public health threat strengthened public acceptance of the technology. It is notable that in the event of a crisis the Stanford OTL licensing records could have provided a ready list of companies.

From our analysis, the goal of providing appropriate incentives so that genetic engineering technology could be commercialized for public use and benefit in an adequate and timely manner certainly was realized. Two thousand four hundred and forty two known products were developed from the recombinant DNA technology, among them drugs to mitigate the effects of heart disease, lung disease, anemia, HIV-AIDS, cancer, diabetes, and numerous other diseases and disorders. The Cohen-Boyer patents covered a fundamental new platform technology, and the way in which they were licensed, provided broad access for firms to develop marketable products. Hundreds of small biotech firms were founded on the recombinant DNA technology, some of which have grown into large and successful firms. Small companies gained legitimacy through licensing the Cohen-Boyer patents, making it easy for them to attract funding and strategic alliances.

Certainly some of this success is a function of the larger historical context: the Cohen-Boyer patents were issued at the crux of several precedent-setting developments in the judicial, legislative, and economic spheres. The June 1980 Supreme Court ruling on *Diamond v Chakrabarty*, a landmark 5-4 decision, made the patenting of life forms possible with its oft-quoted phrase, "anything under the sun, that is made by man."⁹⁰ This decision had a tremendous impact on the ability of inventors to patent genetically engineered life forms, hitherto an unexplored commercial region. The December 1980 Bayh-Dole Act gave non-profit and small business research institutions intellectual property rights over discoveries from federally-funded research. Because the vast majority of university researchers were funded through the NIH, the National Science Foundation (NSF), and other government mission agencies, the Bayh-Dole Act greatly strengthened the incentives for universities to patent their discoveries systematically.⁹¹

⁹⁰ The Committee Reports accompanying the 1952 Act inform us that Congress intended statutory subject matter to "include anything under the sun that is made by man." S. Rep. No. 1979, 82d Cong., 2d Sess., 5 (1952); H. R. Rep. No. 1923, 82d Cong., 2d Sess., 6 (1952).

⁹¹ One other thing that was changing at Stanford at this time was in fact *who* got patent rights. Stanford and Wisconsin had a fairly regular practice of allowing their faculty to take out patents. This meant that

This was particularly important at that time, just before the rise in private pharmaceutical and biotechnology R&D that began in the 1980s. The Bayh-Dole Act also gave incentives to Stanford researchers to patent their inventions. Whereas before, the researcher was responsible for any costs during the patenting process, the Bayh-Dole Act codified the ownership by institutions, thus making the institutions responsible for ensuring commercialization. The third development was economic: the venture capital industry was looking for new opportunities, and received authority to invest in high-risk startups with changes in pension fund and other institutional investment rules that began in the late 1970s. Venture capital created new sources to fund the development of new companies that were so crucial to the biotechnology industry's growth.

Eisenberg points out “the reason that universities count these patents as successes is not that they helped move the technology out to the private sector for commercial development, but rather that they generated a lot of revenue for the institutions that own them.”⁹² Financial motivation was one of Stanford's goals for the licensing program and a goal that was certainly achieved. Niels Reimer, notes that “..a nonexclusive licensing program, at its heart, is really a tax.”⁹³ Most interestingly, this was a tax that industry was willing to pay. Companies were already using the technology but they were willing to comply with the licensing program because the terms were reasonable. For many small companies, holding a license to use the Cohen-Boyer technology sent a signal that they were a serious player in the emerging industry. It is interesting to look at the effect of the Cohen-Boyer patents in a different light: in terms of the shifting of monopoly rents from patented biologics to the universities. The prices of the commercial products did not decrease at the end of the patent's term, and it seems likely that the companies set prices more or less independently of Stanford's licensing fees. It would be very difficult to argue that companies would have charged less for their end products if they did not have to pay royalties in order to use the technology. In effect, the licensing revenues take the form of a prize that rewards the inventors and their universities for the commercial value

individuals had to pay for it (usually), but Bayh-Dole codified the ownership by institutions, and gave institutions responsibility for ensuring commercialization.

⁹² Rebecca Eisenberg, ‘Public Research and Private Development: Patents and Technology Transfer in Government-Sponsored Research’, *Virginia Law Review*, 82, (1996), 1710.

⁹³ Niels Reimer, Interview Conducted by Sally Smith Hughes in 1997. UC Berkeley, Regional Oral History Office, Program in the History of the Biological Sciences and Biotechnology.

of their discovery. There is no evidence that the licensing costs actually had an effect on the prices of the consumer goods although this is certainly an interesting question.

Stanford made very pragmatic decisions about pricing its intellectual property. Reimers recalled at least one alumnus writing, “You’ve got a patent; you can dominate everything here. Why are you charging such a low royalty? You know Stanford could use the money. Charge a higher royalty.”⁹⁴ But the fact is that the licensing scheme may have been designed to cover some of the flaws of the original patent. When Stanford started thinking about licensing, it was not even clear that the patent would issue; it was very vulnerable. Because there was no world-wide protection of the intellectual property, Stanford had to price the license so that licensing was preferable to litigation. Also, had Stanford opted for an exclusive licensing strategy, other firms would have a strong incentive to break the patent which, given the questions Halluin raised about the patent, they probably could have done with enough resources and persistence. These points may have limited how much Stanford could subsequently charge for the license.

The story of the commercialization of the Cohen-Boyer patents could have developed quite differently. Had Stanford and the University of California taken only financial considerations into account, it is likely that they would have opted for much higher royalty rates or a more lucrative limited use exclusive license. In addition, they might have been aggressive litigants instead of setting up a defensive litigation fund. In retrospect, the venture might have failed at several different points. As it was, Stanford consulted broadly to make sure that they had had consensus, even though the scope of the discovery “clearly dictated, very early, a nonexclusive licensing strategy.”⁹⁵ Recently, David Botstein, a genomics professor at Princeton, reflected⁹⁶:

"Niels Reimers was a genius. And he got it exactly right. That the tools are the things that you encourage the diffusion of by making non-exclusive licenses with a reasonably royalty, and that the products you defend by patents that are exclusive. ... That was brilliant because they made more money than they possibly could any other way. And they diffused the technology. How could you argue with that?"

⁹⁴ Niels Reimers, *Niels Reimers*. Regional Oral History Office, The Bancroft Library, University of California, Berkeley 1997. Available from the Online Archive of California; <<http://ark.cdlib.org/ark:/13030/kt4b69n6sc>>

⁹⁵ Niels Reimers, ‘Tiger by the Tail’, *Chemtech*, 17(8), (1987), 464-471.

⁹⁶ Interview with Professor David Botstein, August 25, 2005. Conducted by Marjorie Gurganus, Robert Cook-Deegan, and Ilse Wiechers

Had it not been for Stanford's enlightened licensing practices, this technology might have been confined to the laboratories of pharmaceutical companies and we might never have seen the rise of a biotechnology industry. Or the technology would have been placed into the public domain, which might have perhaps reduced overall transaction costs. This being said, Stanford and the University of California, would not have accrued the quarter billion dollars they plowed back into research and research infrastructure. On one hand the public lost, but on the other it gained. It would be interesting to trace how those funds were actually used and what additional research was funded internally at the two universities. The Cohen-Boyer patents were precedent-setting in all respects. What we hope to have shown here is that the process Stanford went through was far from straightforward, and far from over once the patents issued. The OTL continued to work on its evolving licensing scheme as new opportunities came to light, and continued to mold its licensing policies to fit the needs of the emerging biotechnology industry.

Recently, universities became more entrepreneurial, looking for different streams of revenue that are not anti-ethical to university values. As a result, a new organized and more professional system of technology transfer has emerged. Certainly the Cohen-Boyer patents were at the heart of the early debate in the evolving system. We can now look back at Stanford's success and think that it was inevitable or easy, but an examination of history reveals many places where Stanford could have behaved opportunistically or taken a wrong turn. Many other universities unsuccessfully pursue intellectual property rights and whether the lack of success is due to improper licensing policies or less marketable inventions, it becomes evident that even with a model technology commercialization is far from simple. The assumption is that Stanford and UC were pursuing revenue alone— this is done without understanding the controversies that faced Stanford at that time, and the creativity and restraint that Stanford had to employ to surmount them. Stanford's licensing program is a good example, not just for its monetary success, but in terms of the process that it set in place.

While many universities have now instituted licensing programs and are aggressively pursuing intellectual property rights, this study demonstrates that this process was not at all easy or straightforward. Stanford was forced to be innovative to accommodate the great uncertainties it faced. Moreover, the process was not finished

when the first licensing agreement was formulated; Stanford's strategies continued to evolve as the times changed, adopting and learning about procedures and working with companies.

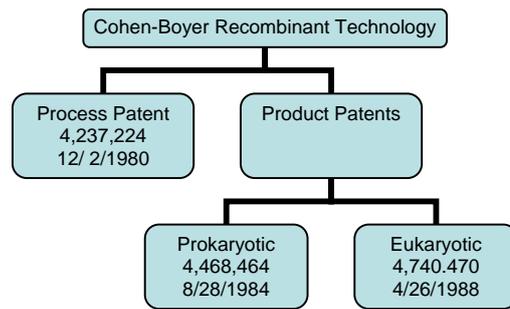


Figure 1: Schematic of Cohen-Boyer Patents

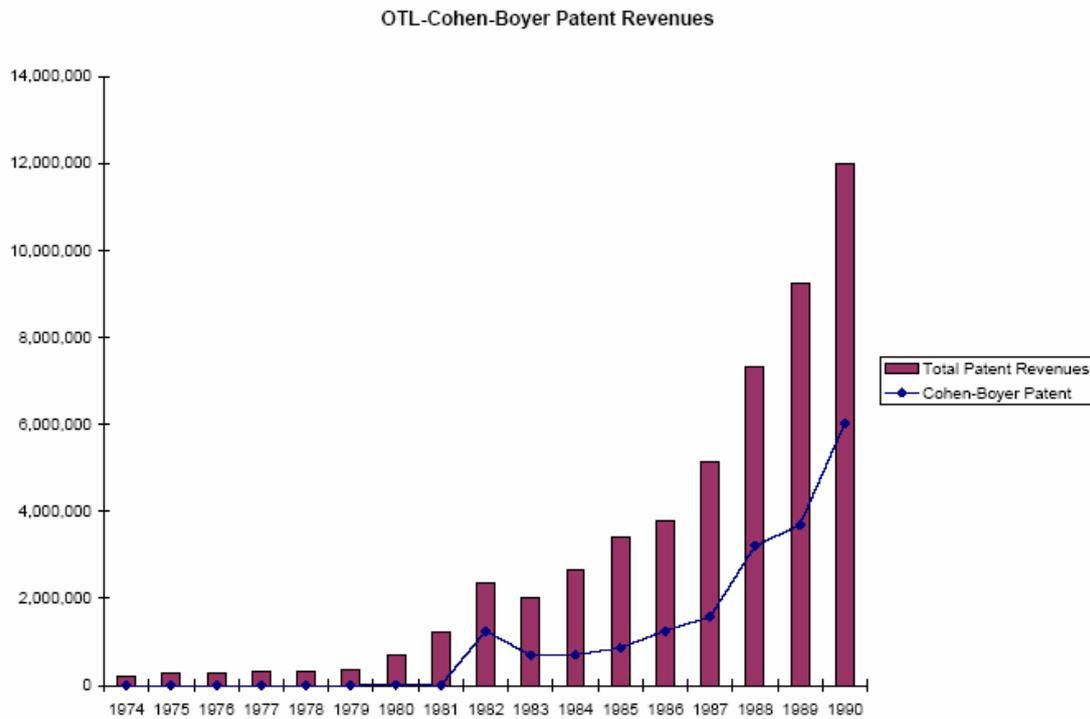


Figure 3: Cohen-Boyer Revenue as a Fraction of Total Stanford Licensing Revenue 1974-1990⁹⁷

Note: In addition to patents, the OTL handles copyrights, primarily for software, and trademark licensing (for example, the Stanford name on T-shirts) and tangible research property, including non-patented biological materials such as a transgenic mouse.

⁹⁷ Timothy Lenoir, 'Biochemistry at Stanford: A Case Study in the Formation of an Entrepreneurial Culture', 21 April 2002.

Table 1 : Cohen Boyer Standard Licensing Agreements History

Version	Effective Date	Sign-up Fee & Minimum Annual Advance (MAA)	Earned Royalty Rates		
			End products	Bulk Products	Basic Genetic Products & Process Improvements
1	12/2/1980	Each \$10,000; with special 5 times credit	Graduated rate: 1% (first \$5M); 0.75% (next \$5M); 0.5% (over \$10M)	Graduated rate: 3% (first \$5M); 2% (next \$5M); 1% (over \$10M)	10% for basic products sales; 10% of cost savings and economic benefits
2	1/1/1982	Each \$10,000	Graduated rate: 1% (first \$5M); 0.75% (next \$5M); 0.5% (over \$10M)	Graduated rate: 3% (first \$5M); 2% (next \$5M); 1% (over \$10M)	
3	8/1/1985	Each \$10,000	Same as above, but started write-in*	Same as above, but started write-in	
4	11/1/1986	Each \$10,000	1%	3%	
5	9/1/1989	Each \$10,000 if < 125 employees; Each \$50,000 if > 125 employees	2%	6%	
<p>* Write-in royalty rates instead of print in effective from August 1985; **Royalty rate for sales made outside U.S. all apply: enjoy the rate of 0.5 % for end products and 1% for Bulk products; 10% for basic products and 10% of cost saving and economic benefits</p>					

Table 2: Non-Standard Licensing Agreement

Effective Date	Type of agreement	Licensee Category	Sign-up fee & MAA	Royalty Rate	Other Highlights
Mid-1991	Alternative License	Small distributor and resellers	No MAA	Doubled to 4% for End Product; 6% for Bulk Product; no changes for non-U.S. sales	No credits toward earned royalty
End of 1994	Research & Development Agreement	No products are expected to be produced for sale	Sign-up payment waived; all future MAA as one time payment	NA	20% of discount offered
December 1996	Final Year	Final year sign-up	No sign-up fee of \$10,000; MAA is prorated and payable upon execution	NA	

Table 3: Distribution of Revenue by Licensing Agreement

License Version	Effective Date	Number of Companies Signed	Revenue (Share)
1	12/2/1980	85 ⁹⁸	\$215,663,697 (84.66%)
2	1/1/1982	15	\$14,229,566 (5.59%)
3	8/1/1985	11	\$3,338,347 (1.31%)
4	11/1/1986	21	\$5,355,889 (2.1%)
5	9/1/1989	Small	\$12,120,719 (4.76%)
		Large	\$2,630,195 (1.03%)
Alternative Agreement	Mid 1991	58	\$740,070 (0.29%)
R &D Agreement	End of 1994	51	\$630,069 (0.25%)
Final Year	December 1996	6	\$39,680 (0.02%)
Total		468	\$254,748,232

⁹⁸ Originally only 73 companies signed up; however, due to the merger and acquisition, there are additional 12 companies inherited the original license date of December 2, 1980.

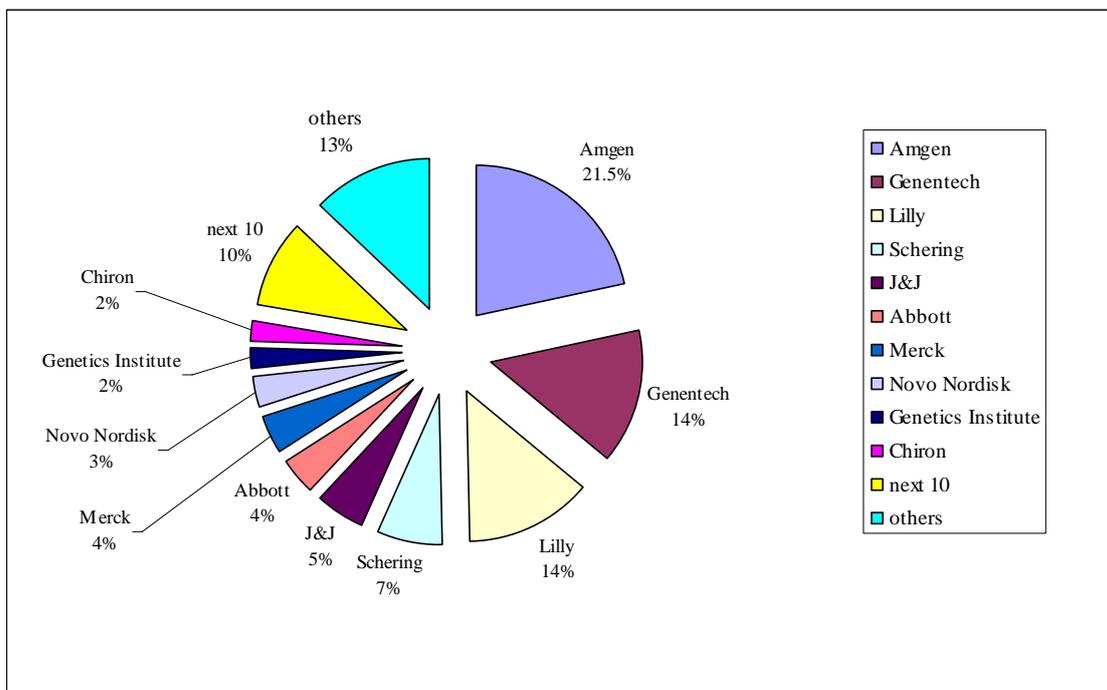
Figure 4: Distribution of Royalties

Table 4: Distribution of Cohen-Boyer Licensees by Industry Sector

Industry Sector	Licensees	Revenue (Share)	Companies paying earned royalties (%)
Biotechnology	325	\$133,617,842 (52.45%)	87 (28%)
Pharmaceutical	58	\$111,858,010 (43.9%)	22 (38%)
Chemical	31	\$3,210,954 (1.26%)	7 (23%)
Agriculture	16	\$3,208,373 (1.26%)	2 (13%)
Food	14	\$1,537,585 (0.6%)	3 (21%)
Diagnostic	8	\$761,976 (0.3%)	2 (25%)
Energy	3	\$133,334 (0.05%)	0 (0%)
Instrumentation	3	\$149,059 (0.06%)	0 (0%)
Veterinary	2	\$150,000 (0.06%)	0 (0%)
Engineering	1	\$20,000 (0.01%)	0 (0%)
Environment	1	\$40,000 (0.02%)	0 (0%)
Miscellaneous	6	\$61,099 (0.02%)	2 (33%)
Total	468	\$254,748,232	125 (27%)

Table 5: Blockbuster Drugs of Top Ten Licensees of Cohen-Boyer Patent

Company	License Date	Paid Royalties	Product Trade Name	Date Approved	Year started to pay Earned Royalties
Amgen	12/2/1980	\$54,783,507	Epogen	June 1989	FY 1989-1990
			Procrit ⁹⁹	December 1990	
			Neupogen	February 1991 June 1994 December 1994 December 1995	
Lilly	12/2/1980	\$36,685,982	Humulin ¹⁰⁰	October 1982	FY 1983-1984
			Human trope	March 1987	
			Abciximab ¹⁰¹	December 1994	
			Humalog	June 1996	
Genentech	12/2/1980	\$34,737,780	Humulin ¹⁰²	October 1982	FY 1985-1986
			Protropin	October 1985	
			Roferon A ¹⁰³	June 1986 November 1988	
			Activase	November 1987	
			Nutropin	November 1993 March 1994 December 1996 December 1997	
			Pulmozyme	December 1993 December 1996	
			Nutropin AQ	December 1995 December 1995	
			Actimmune	December 1990	
Kogenate	February 1993				
Schering	12/2/1980	\$17,960,351	Intron A ¹⁰⁴	June 1986 June 1988 November 1988 February 1991 July 1992 December 1995	FY 1986-1987
Johnson & Johnson	12/2/1980	\$13,418,280	Procrit ¹⁰⁵	December 1990	FY 1992-1993
Merck	12/28/1984	\$10,085,657	Recombivax HB ¹⁰⁶	July 1986	FY 1986-1987
Abbott	12/2/1980	\$9,804,444	Various in vitro HIV diagnostics	1985, 1989 and 1992	FY 1987-1988
Novo-Nordisk	12/2/1980	\$8,669,119	Novolin	May 1991	FY 1990-1991
Genetic Institute	12/2/1980	\$5,946,978	Recombinate	December 1992	FY 1993-1994
Chiron	12/2/1980	\$5,099,071	Proleukin	May 1992	FY 1987-1988
			Betaseron ¹⁰⁷	August, 1993	

⁹⁹ Partnered with Ortho and Johnson and Johnson.

¹⁰⁰ Partnered with Genentech.

¹⁰¹ Partnered with Centocor.

¹⁰² Partnered with Lilly.

¹⁰³ Partnered with Roche.

¹⁰⁴ Partnered with Biogen.

¹⁰⁵ Partnered with Amgen and Ortho

¹⁰⁶ Partnered with Biogen.

¹⁰⁷ Partnered with Berliex