Lessons from the Commercialization of the Cohen-Boyer Patents: The Stanford University Licensing Program

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ABSTRACT

The Cohen-Boyer licensing program, by any variety of metrics, was widely successful. Recombinant DNA (rDNA) products provided a new technology platform for a range of industries, resulting in over US$35 billion in sales for an estimated 2,442 new products. Over the duration of the life of the patents (they expired in December 1997), the technology was licensed to 468 companies, many of them fledgling biotech companies who used the licenses to establish their legitimacy. Over the 25 years of the licensing program, Stanford and the University of California system accrued US$255 million in licensing revenues (to the end of 2001), much of which was subsequently invested in research and research infrastructure. In many ways, Stanford's management of the Cohen-Boyer patents has become the gold standard for university technology licensing. Stanford made pragmatic decisions and was flexible, adapting its licensing strategies as circumstances changed.

1. INTRODUCTION

The licensing of the Cohen-Boyer patents by Stanford University represents one of the most successful university technology licenses. The discovery covers the technique of recombinant DNA and allows for the useful manipulation of genetic material. Examining Stanford's licensing of the intellectual property is best understood in context and as part of the university's larger strategy. Moreover, designing and setting up the licensing program involved uncharted territory at that time. The first patent issued on December 2, 1980, after 6 years under review at the U.S. Patent and Trademark Office: the original application was filed in November 1974. This date was two weeks before the effective date of the Bayh-Dole Act, which assigned intellectual property (IP) rights over faculty discoveries from federally funded research to universities and emphasized the university's responsibility for commercialization.[1] The intention was to provide a means for economic growth, technological change, and enhanced U.S. competitiveness.

The Cohen and Boyer's discovery provided tools for genetic engineering and was the subject of controversy that led to a lively public debate during the decade of the 1970s. Sally Smith Hughes documents Cohen and Boyer's scientific discovery, Stanford's decision to pursue patents, and the public controversies surrounding recombinant DNA.[2] The debate was symbolically resolved with the June 1980 U.S. Supreme Court ruling on *Diamond v Chakrabarty*, a landmark 5–4 decision, which made the patenting of life forms possible with the Court's oft-quoted clause, "*anything under the sun, that is made by man*." This decision cleared the way for the Cohen-Boyer application, which covered a fundamental technique, with the potential to become a platform technology that essentially led to a new paradigm in biotech research.

Feldman MP, A Colaianni and C Liu. 2007. Lessons from the Commercialization of the Cohen-Boyer Patents: The Stanford University Licensing Program. In *Intellectual Property Management in Health and Agricultural Innovation: A Handbook of Best Practices* (eds. A Krattiger, RT Mahoney, L Nelsen, et al.). MIHR: Oxford, U.K., and PIPRA: Davis, U.S.A. Available online at www.ipHandbook.org.

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Of course, once the patent was granted, Stanford University, as the assignee, was required to design a licensing program that would be consistent with the public-service mission of the university and provide sufficient incentives for private industry to invest the requisite resources to bring products to market while producing revenue for the university. Feldman, Colaianni and Liu[3] detail the history of Stanford's licensing program, focusing on the process and the logic that guided the commercialization regime. Given the early controversy surrounding the Cohen-Boyer patent, the eventual success required a great deal of creativity, strategy, and persistence. Certainly, the professionals involved all contributed to the success, from Donald Kennedy, then president of Stanford, Robert Rosenzweig, then vice president for public affairs, Nils Reimer, founding director of the Stanford Office of Technology Licensing (OTL) to Katherine Ku, then licensing associate and current director of the OTL.

The purpose of this chapter is to summarize lessons learned from Stanford's design and implementation of the Cohen-Boyer licensing program. Many universities attempt to emulate Stanford University's success at technology transfer; however, there is a limited appreciation for the high degree of creativity and adaptability of the Stanford Office of Technology and Licensing (OTL) in setting up its licensing program and making the myriad decisions that guided the ultimate outcome. In spite of many obstacles, Stanford University pursued the recombinant DNA patents and designed a strategy that met the public-service goals of the university by broadly licensing the technology; provided incentives for private companies to commercialize derivative products; and contributed to the creation of an innovation system that benefited Silicon Valley and reached across the American economy.

2. A LIST OF LESSONS LEARNED FROM COHEN-BOYER

2.1 *Keep wider university goals in mind*

Despite the economic success of the licensing program, profit was not the primary motive. Stanford University had four goals that guided the development of the Cohen-Boyer license:

- to be consistent with the public-service ideals of the university
- to provide the appropriate incentives in order that genetic engineering technology could be commercialized for public benefit in an adequate and timely manner
- to manage the technology in order to minimize the potential for biohazard
- to provide income for educational and research purposes

Robert Rosenzweig, vice president for public affairs at Stanford, in a 1976 open letter addressed to "*Those Interested in Recombinant DNA,*" wrote "*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 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.*"

The balance of financial objectives against other goals is further demonstrated when Stanford decided not to pursue extending the patent life. The original 1974 patent application had claimed both the process of making recombinant DNA and any products that resulted from using that method. These applications were subsequently divided into the process patent and two divisional product applications: one claimed recombinant DNA products produced in prokaryotic cells and the other claimed the products in eukaryotic cells. Stanford filed a terminal disclaimer, which meant that all subsequent applications 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.[4] 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 date. This limited Stanford's collection of royalties because of the time delay inherent in commercialization, especially of pharmaceutical

products. Stanford honored its obligation to the licensees with the realization that, as Kathy Ku wrote at the time "*...it would not be good public policy or public relations if we were to ask for or even get such an extension.*"

Stanford did not require other nonprofit research institutions to take a license in order to use the technology. Niels Reimers and Kathy Ku report that the thought of licensing the technology out to other nonprofit research institutions had never entered into discussions about the licensing program. This licensing practice established a research exemption, or research-use exemption, which is consistent with the norms of open science,[5] and stands in contrast to recent developments in research-use exemption policies, such as *Duke v. Madey* and the WARF stem-cell licensing program.[6]

To summarize, engaging in commercial activity encourages higher education institutions to act like for-profit entities. Intellectual property has no value unless it is defended. Stanford set up a litigation reserve fund that provides a credible threat of enforcement of the license. Despite several attempts to withhold payments from a variety of large and small companies plus one attorney who made challenges to the patents a "hobby," Stanford was able to settle these disputes informally and without formal litigation. This stands in contrast to the recent upswing in litigation by U.S. universities, including a recent law suit filed by the University of Alabama to prevent an artist from using the universities athletic colors.

2.2 *Consult widely to build consensus*

While intellectual property typically involves limited disclosure, Stanford University engaged in a pattern of consulting widely across various stakeholders to achieve consensus and to ensure that its actions were supported. For example, Rosenzweig worked to achieve consensus with both the faculty and the National Institutes of Health (NIH) as the sponsoring agency. In a 1976 open letter, he asked the faculty to comment on whether the university should proceed with the patent process. Rosenzweig also sent a letter to Donald Fredrickson, NIH director, asking his opinion on patenting the Cohen-Boyer discovery and enclosed a copy of the memorandum sent to faculty. Fredrickson responded by sending a mass mailing to "a broad range of individuals and institutions," asking them for their comments on the patent question. [7] Fredrickson's letter laid out five possible alternatives that NIH could take regarding recombinant DNA patenting and subsequent licensing: In response, Fredrickson received approximately 50 letters.

A compromise consensus emerged from among a list that Frederickson generated that Stanford should be able to patent recombinant DNA research but with nonexclusive licensing. A nonexclusive license ran counter to economic logic, contrary to the subsequent preferences articulated in the Bayh-Dole, Act and ignored petitions from Genentech and Cetus who stood to gain from exclusive licenses. The logic was that rDNA was a platform technology and that any one company could not exploit all the possible applications. Broad nonexclusive licensing not only contributed to the economic success of the patents but also created a population of companies who drove the technology forward.

There are other instances when Stanford sought transparency that was consistent with the actions of a university. While applicants generally keep patent applications secret from the date they are filed until they are granted and therefore protected, Stanford opened the patent prosecution file to the public. This was an unusual move that was consistent with reducing subsequent questions about the technology and was also consistent with the public mission of the university.

Stanford engaged in an open process that attempted to build consensus across a wide range of stakeholders. While the university did stand to profit from the licensing program, their actions were consistent with the university's larger and more traditional societal goals.

2.3 *Don't behave opportunistically*

The most successful university technology transfer involves relationships that develop over time. Signing a licensing agreement represents a transaction that is a first step in a relationship that requires maintenance and oversight. Each licensee received an annual letter from the Stanford OTL.

That went a long way in establishing long-term relationships and encouraging dialogue.

When Stanford initiated its licensing program, no precedent existed for specific licensing terms of the IP. Keeping with its practice of consulting widely and building consensus, Stanford interviewed a variety of companies representing different markets when the license terms, particularly the royalty rates on end products, were being formulated. Through this effort, licenses were pre-sold and unrealistic terms were avoided. To make the licensing process easier, the OTL took great pains to categorize the different potential recombinant DNA products and to offer appropriate royalty rates. 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 the visibility of the licensee's product and the expected revenue from each license, the OTL encouraged compliance. A graduated royalty system ensured that smaller companies weren't penalized with low sales volume.

Stanford made pragmatic decisions about pricing its intellectual property and kept the annual fees and royalty rates reasonable. While this might have reflected a strategy to deal with some of the weaknesses with the patent, the university could have been greedy and pursued higher rates. Nils 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.*"[8] This advice was not taken. The rates that were chosen were selected after consultation with industry about accepted practices and did not exploit the university's monopoly position.

Furthermore, Stanford created special provisions for lower licensing fees and royalty rates for small firms in 1989. At this time, 209 fledging biotech firms, most of them in the San Francisco Bay Area, signed licensing agreements.

2.4 *Be flexible and experiment*

Over the 17 years of the licensing program Stanford experimented with five versions of the standard license agreements and provided three special licensing agreements. A total of 468 companies licensed the Cohen-Boyer technology. Licensing the patents was very much a learning process that balanced the capabilities of companies, especially in the embryonic biotech industry, with the economic potential of the technology. 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.*"[9] Table 1 summarizes the various licensing regimes and the number of companies that signed up under each version. Certainly the economic impact would have been less without this flexibility and adjustments.

The first version of the license provided two incentives to encourage companies to sign up. Remember that the technology was already in the public domain through publication and that the open patent files and companies were already using rDNA. It was not clear that companies would comply with the terms. The first incentive for companies to take a license in 1981 was a credit toward future royalties over the first five years, up to a total of US$300,000. The second incentive came when companies were advised that the licensing terms would change and encouraged them to sign up early. In response to this news, 82 companies signed up. The largest share of earned royalties from product sales accrued to these firms.[10]

The first license's terms were a US$10,000 up-front fee with a minimum annual advance (MAA) of US$10,000. Earned royalty rates on products were provided on a graduated basis for bulk products, end product sales, and process improvements on existing products based on production cost savings. Under the licensing agreements, Stanford received unprecedented royalties on downstream drug sales in a stipulation known as *reach-through* licensing: Stanford received end-product royalties based on a percentage of final product sales. The Cohen-Boyer IP rights extended to all products developed using the technology. If companies did not sign a license agreement, any end products they developed that used rDNA could potentially be contested.

Table 1: Cohen-Boyer Standard Licensing Agreements History (in U.S. dollars)

Version	Effective date	Sign-up fee & minimum annual advance (MAA)	Earned-royalty rates			Number of companies signed	Revenue (share)
			End products	Bulk products	Basic genetic products and process improvements		
1	12/2/1980	Each $10,000; with special five 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	73	$215,663,697 (84.66%)
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)		15	$14,229,566 (5.59%)
3	8/1/1985	Each $10,000	Same as above, but started write-in	Same as above, but started write-in		10	$3,338,347 (1.31%)
4	11/1/1986	Each $10,000	1%	3%		21	$5,355,889 (2.1%)
5	9/1/1989	Each $10,000 if < 125 employees; Each $50,000 if > 125 employees	2%	6%		209	$12,120,719 (4.76%)
Alternative license	Mid-1991	No MAA	4%	6%	N/A	12	$2,630,195 (1.03%)

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Table 1 (continued)

R & D agreement	End of 1994	Sign-up payment waived; all future MAA as one-time payment	N/A	N/A	NA	36	$553,083 (0.22%)
Final year	1996	No sign-up fee of $10,000; MAA is prorated and payable upon execution	N/A	N/A	NA	6	$39,680 (0.02%)

The second standard licensing agreement dropped the royalty-credit incentive and an additional 15 companies signed the agreement. In August 1985, the OTL issued its third standard version of the license agreement, which allowed for negotiation by providing a space to write in agreed-upon rates. In practice, though, the earned-royalty rates were almost always at the same graduated rates that were used in the second version. This fact may be attributed to the sharing of information among potential licensees about prevailing terms and what terms might be expected. Another ten firms signed up under this licensing agreement. Another adjustment was made in November 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 version and reflected the realization that the patents could earn higher rates. In response, perhaps motivated by the possibility of further increases in the future, 21 more firms signed licensing agreements. The fifth version of the Cohen-Boyer standard licensing agreement, adopted in September 1989, demonstrated further strategic changes. In order to encourage licensing by small start-up companies, consideration of company size was introduced. For companies with fewer than 125 employees, the sign-up fee and MAA fee remained the same, at US$10,000 each. The strategy worked—209 small biotech firms became licensees under this version, along with 12 large companies.

In addition to the standard agreements, there were three nonstandard licensing agreements that provided alternative agreements, making sure that Stanford could collect as much revenue as possible without being unfair to companies with special circumstances. The first was an alternative license for small distributors or resellers of recombinant DNA products. Fifty companies signed on under this alternative agreement, accounting for 17.5% of the total 275 licensees signed after 1991 and providing US$462,000 in licensing revenue. At the end of 1994, a research and development license agreement, with greatly reduced rates, was developed to encourage start-ups that would not realize product sales within the patent lifetime. Another 39 companies signed the research and development license agreements, and, although these licenses did not yield much licensing revenue, they were important to the legitimacy of the small companies. A third nonstandard licensing agreement was offered in the final year to tie up a few loose ends.

In total, the Cohen-Boyer licenses generated US$254 million in revenue during its 17-year term. The initial sign-up and annual fees generated US$26 million, which was 10% of the total licensing income. The licensing program certainly would have been less successful without these revisions and accommodations. A whopping 90% of the total revenue (US$228 million) was from royalty income from product sales. This mirrors the commercial success of recombinant DNA products.

2.5 *Technology transfer is all about skewed distributions*

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 that licensed the recombinant DNA technology and their products demonstrates that even within a single license, highly skewed outcomes account for the high revenues. Commercial products developed by the licensees generated over US$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 expired in December 1997, reflecting a range of applications in a variety of industries.[11] Starting in 1991, 400 new products, on average, were being brought to the market every year. Recombinant DNA product sales reached US$500 million dollars in 1987 and then doubled from 1988 to 1990. Sales doubled again from 1991 to 1994 and yet again from 1994 to 1998.

The revenue received from each of the Cohen-Boyer licensees ranged from US$4.24 million to US$54.78 million dollars. Of the 468 licensees of Cohen-Boyer technology, ten companies alone provided 77% (US$197 million) of the total licensing income. One company, Amgen, accounted for over one-fifth of the total revenues received

under the licensing program. Figure 1 provides a breakdown of the royalty share provided by different companies.

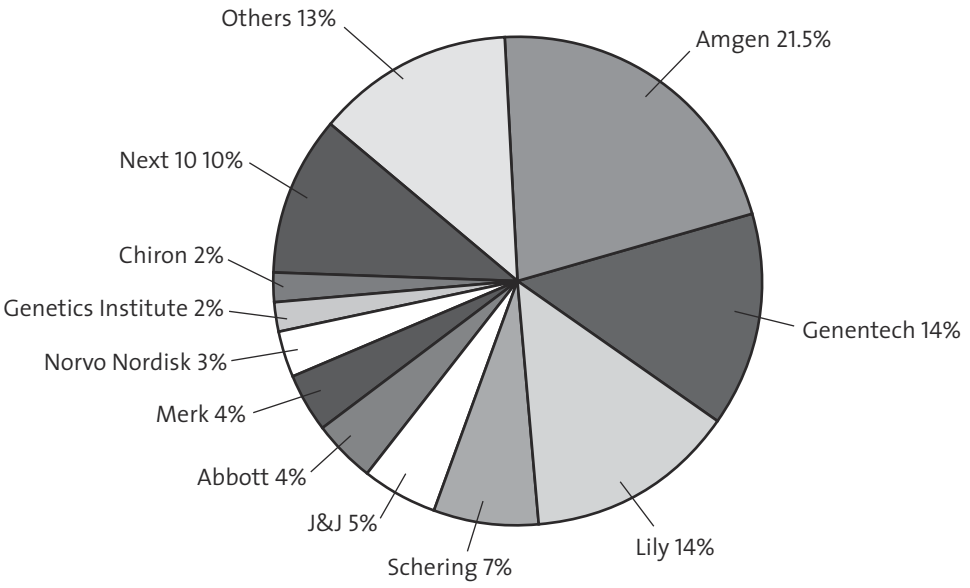
Table 2 lists these ten companies and the products developed under the license. Many of the products were developed under strategic alliances between start-up biotech firms and large pharmaceutical firms, or between biotech firms. All of the top-ten companies, except Merck (which signed the agreement in 1984) signed the first standard agreement in December 1980. The next 10 companies accounted for another 10%, while the remaining companies generated less than 13% of total royalty revenue.

3. CONCLUSIONS

In the 1970s, universities became more entrepreneurial, looking for different streams of revenue that supported the university's mission. As a result, a new system of technology transfer emerged. Certainly the Cohen-Boyer patents and Stanford University's licensing program were at the heart of the debate and central to the evolving system.

It would be a mistake to look back at Stanford's success with the Cohen-Boyer licenses and think that its success was inevitable or that the licensing process was easy. An examination of history reveals many episodes where Stanford University could have behaved opportunistically or taken a wrong turn. The mistaken notion that Stanford and the University of California system were pursuing revenue as a primary goal ignores the controversies that faced Stanford at that time and the creativity and discipline that Stanford had to employ to surmount them. Stanford's licensing program is a good example, not just in terms of its monetary success, but in terms of the lessons it affords to others who work in the area of licensing and technology transfer. While many universities have now instituted licensing programs and are aggressively pursuing intellectual property rights, our study demonstrates that this process is not at all easy or straightforward. In retrospect, Stanford's licensing venture might have failed at several turns and Stanford was forced to be innovative to accommodate the great uncertainties it faced. Had Stanford and the University of

Figure 1: Distribution of Royalties



Source: Compiled by the authors.

Table 2: Blockbuster Drugs of Top Ten Licensees of Cohen-Boyer Patent

Company	Paid royalties (US dollars)	Product trade name	Year started to pay earned royalties
Amgen	$54,783,507	Epogen Procrit [a] Neupogen	FY 1989–1990
Lilly	$36,685,982	Humulin [b] Humantrope Abciximab [c] Humalog	FY 1983–1984
Genentech	$34,737,780	Humulin [d] Protropin Roferon A [e] Activase Nutropin Pulmozyme Nutropin AQ Actimmune Kogenate	FY 1985–1986
Schering	$17,960,351	Intron A [f]	FY 1986–1987
Johnson & Johnson	$13,418,280	Procrit [g]	FY 1992–1993
Merck	$10,085,657	Recombivax HB [h]	FY 1986–1987
Abbott	$9,804,444	Various in vitro HIV diagnostics	FY1987–1988
Novo-Nordisk	$8,669,119	Novolin	FY 1990–1991
Genetic Institute	$5,946,978	Recombinate	FY 1993–1994
Chiron	$5,099,071	Proleukin Betaseron [i]	FY 1987–1988

a. Partnered with Ortho and Johnson and Johnson.
b. Partnered with Genentech.
c. Partnered with Centocor.
d. Partnered with Lilly.
e. Partnered with Roche.
f. Partnered with Biogen.
g. Partnered with Amgen and Ortho.
h. Partnered with Biogen.
i. Partnered with Berliex.

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. Stanford made very pragmatic decisions about pricing its intellectual property. In addition, it might have had to aggressively litigate instead of playing a defensive litigation strategy. Moreover, the process was not finished once the first licensing agreement was formulated; Stanford made pragmatic decisions and proved flexible, adapting its licensing strategies as circumstances changed.

Had it not been for Stanford's enlightened licensing practices, the Cohen-Boyer technology might have been placed in the public domain where the technology could have remained undeveloped or in the laboratories of large established pharmaceutical companies. Or it might have been licensed exclusively and the rise of a biotechnology industry might have been delayed for years or decades. Small companies gained legitimacy through licensing the Cohen-Boyer patents, making it easy for the companies to attract funding and strategic alliances. Hundreds of small biotech firms were founded on the recombinant DNA technology, some of which have grown into large and successful firms. In total, 2,442 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. Stanford and the University of California received a quarter of a billion dollars that was used to fund internal research and provide infrastructure. It would be interesting to trace how those funds were actually used and what additional benefits may thus have been generated.

Stanford University's licensing program still provides a reference point for the future practices of university technology transfer. While the amount of licensing revenue received and the value of the commercial product generated are awe inspiring, it should be remembered that this process was neither easy nor straightforward. The Stanford OTL was very creative and adaptive in designing their licensing program. They never lost sight of their larger goals to society and to the scientific enterprise.

ACKNOWLEDGEMENTS

This work was supported in part by the Center for Public Genomics, Duke University, under grant P50-HG003391 from the National Human Genome Research Institute and the U.S. Department of Energy.

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1 Previously, individual faculty members had been able to file patents, negotiating the IP (intellectual property) rights with the federal agency that had sponsored the research.

2 Hughes SS. 2001. Making Dollars out of DNA. The First Major Patent in Biotechnology and the Commercialization of Molecular Biology, 1974-1980. *Isis* 92:541-75.

3 Feldman MP, A Colaianni and C Liu. 2006. Commercializing Cohen-Boyer: 1980-1997. Unpublished.

4 "The Patent Office often requires terminal disclaimers to prevent an applicant seeking to extend patent life from filing continuation applications." See Reimers N. 1987. Tiger by the Tail. *Chemtech* 17(8):464–71.

5 The OTL *did* recognize and account for, in their subsequent licensing programs, 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.

6 The Wisconsin Alumni Research Foundation (WARF), in 2002, signed its first licensing agreement, for stem cells, with a commercial provider and also signed a separate license agreement permitting U.C.-San Francisco, an academic provider listed on the NIH registry, to distribute human embryonic stem cells worldwide for use in research.

7 Letter from Donald Fredrickson to Robert Rosenzweig, dated 2 March 1978. Obtained from: United States. Office of the Director, NIH. Recombinant DNA Research: Documents Relating to "NIH Guidelines for Molecules,"

June 1976 to November 1977. Department of Health, Education, and Welfare (DHEW).

8 Ibid.

9 Ku K. 1983. Licensing DNA Cloning Technology. Presented at the LES USA/Canada Central/Western Regional Meeting, Scottsdale, Arizona, February. A copy was obtained from the Stanford University OTL, 17 August 2004.

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

11 Compiled from OTL Archives.