Licenses As Critical Sources Of Innovation

Part 2: Medical Progress

By Viktor Braun

In financially and economically unstable times, when stock markets become rollercoasters, apparent safe-havens such as mortgage lenders or re-insurance companies tumble and fall like cardboard houses, and economies across the world are on the brink of falling into deep recessions, it is natural for humans to search for comfort and stability in other realms of life. While nature, our bodies and the societies we have created operate in cycles, which occasionally lead to both positive and adverse extremes, there is a component of human evolution that has been remarkably strong and consistent in its upward pursuit: Technology. While due to the daunting demographic developments in many countries there are dark clouds of doubt about personal and national wealth progression, very few people would seriously question whether the world of tomorrow will be more technologically advanced. In this light, it is worth exploring where technological innovations originate from and how companies can develop promising R&D relationships.

In the previous part of this investigation as to the importance of licensing as a fruitful R&D instrument (*les Nouvelles* December, 2008 issue), we explained how the traditional view of licenses as commercialization instruments was incomplete. By demonstrating how licenses enabled Japan to become one of the worlds' most technologically advanced nations, we indicated the potential of such agreements. In this part, we will show how licenses have contributed to the enhancement of human health. To this end, we will scrutinize the development of drugs, insulin and computerized dentistry. In part three, the final of this series, we will end our journey with a consideration of numerous revolutionary technologies, from the steam engine to the photocopier, as well as with a summary of lessons learned.

As a reminder, a license is the contractual permission to use another party's intellectual property (IP). In practice, the spectrum of technology licensing relationships varies from the right to use another's software to profound R&D relationships involving multiple parties, numerous patents and profound mutual know-how transfers. By allowing another party to use their patented technology and know-how while deciding not to stifle their incentives through non-modification or very strict grant-back clauses, a licensor can substantially enhance the potential of the licensee to improve the respective technology. Employing and commercializing the licensed technology, furthermore gives the licensee access to potentially valuable market feedback. Apart from the opportunity to ascertain what the market desires, a fascinating stream of research has demonstrated that in fields as diverse as electronic circuit boards, sport and leisure goods or software, the users of such products have been critical sources of improvements (von Hippel 2005, Nagel 1993, Voss 1985). Building close customer relationships can therefore provide a greater boost to the innovative potential of licensees.

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Such theoretical discussion has to be evidenced by concrete examples. Technology has arguably had the most direct effect on the human species in the medical realm. Both the duration and quality of human lives have been enhanced substantially over the last centuries by medical progress. Commencing with the pharmaceutical industry, followed by the development of insulin and a case study in the area of medical devices, we will explore the role of innovation through licensing transactions in the medical world.

The development of new pharmaceutical products is characterized by very long, complicated and expensive R&D processes. According to industry estimates it takes between 10-15 years and costs well over a billion dollars to create a new drug, partly as safety, purity, potency and efficacy all have to be demonstrated to the satisfaction of the requisite regulatory body (PhRMA 2008, Louie 2001). As the necessary investments and time to market have risen substantially over the last decades, pharmaceutical companies in general are no longer able to pursue the whole product development cycle themselves while still maintaining a balanced portfolio. The amount of collaborations, especially between large pharmaceutical companies and specialized, dynamic (biotechnology) firms, has skyrocketed and innovation networks have been formed (Suarez-Villa 2004, Piachaud 2004).

Licensing plays a decisive part in this trend and according to Bills (2004), amounts to the most common commercialization method in the biotechnology industry. These types of licenses are often more than just commercialization vehicles and instead can be considered to be "forms of outsourcing" (Piachaud 2004; p. 76). As an illustration of the increasing importance of licenses take Merck & Co., one of the world's largest pharmaceutical companies. While prior to 2000 it closed on about 10 licensing deals per year, from 2004 to 2007 the company signed 50-55 such transactions annually (Merck 2007 and 2004).

It has become standard industry practice to utilize licenses to specifically generate and develop innovations (Arora et al. 2002, Contractor 2002, Anand & Khanna 2000). Promising research from other institutions is licensed-in to further enhance it and bring it through the requisite regulatory stages. This "division of labor" (Piachaud 2004; p. 70) is necessary to share the involved risks and expenses and to benefit from the other company's specialized know-how and research facilities. As a brief example, take the field of drug administration. It often occurs that a beneficial treatment method is discovered, such as lengthy intravenous infusion, which proves cumbersome to administer. In such a case it would make sense for a company to license its patents to a company such as mdRNA, which possesses expertise in the field of intranasal delivery, in order to jointly develop and commercialize an alternative administration method.

There are obviously different kinds of collaboration mechanisms involving licensing prevalent in the industry. Co-promotion involves the licensing of the respective rights from one firm to another, although the marketing takes place under only one trade name with one company making the final decisions. Co-marketing is similar in that it also involves the licensing of the respective rights, but it differs in that the involved companies can market the drug independently. Finally, co-development involves two or more companies jointly creating a new drug. This final form of collaboration is an extensive licensing to innovate scenario, where the parties attempt to mutually optimize the product R&D process. This often includes extensive mutual know-how flow-backs and joint development committees.

At this stage, specific examples are needed to demonstrate the potential of licenses. The first two were identified through interviews with the German pharmaceutical company Bayer. The first case is about Nexavar, in which an increasingly prevalent R&D contract turned out to be mutually beneficial for both parties. In the second, the Adalat case, a licensee collaborated with a third party to substantially enhance the drug in question.

Nexavar

The co-development license agreement between Onyx Pharmaceuticals, at the time a small biotechnology company, and Bayer AG, signed in 1994, involved the development of a new cancer treatment. While Onyx possessed extensive know-how in the field, it lacked the financial means to pay for the expected $500-700 million needed to develop a commercially feasible product. It therefore negotiated a complex joint-development licensing contract with Bayer. Onyx secured itself the right but not the obligation to obtain up to 50 percent of the rights to the final product if they could obtain the finances needed for the R&D. Such practice led to a real R&D licensing partnership in which both parties shared risks and know-how. While Bayer in particular was able to obtain a substantial amount of know-how from Onyx in the field of cancer treatment, which it had previously neglected for numerous years, the joint research team was able to identify a promising development candidate. The resulting drug, Nexavar (sorafenib), received very positive clinical study results and in 2005 was approved by the FDA for the treatment of kidney cancer (Bayer Annual Report 2005). While Bayer manufactures the drug, both parties jointly commercialize.

Realizing the potential of their treatment, the parties invested further sums into its application in the fight against other types of cancer. Since the fall 2007, Nexavar has been approved as a liver cancer therapy in both the U.S. and the EU (*Onyx Annual Report* 2007). Sales of Nexavar have exploded recently and given the rapid quarterly growth in sales, it is well on its way to blockbuster status, which refers to the generation of over a billion U.S. dollars in revenues per year (Leuty 2008).

Adalat

This is a less common example of tripartite innovation made possible by the licensee. In the mid 1980s Bayer's product portfolio contained an anti-infective, cardiovascular drug called Adalat. After considerable original difficulties in finding a collaboration partner, Bayer finally signed a licensing agreement with Pfizer, giving the latter exclusive marketing rights in the U.S. Pfizer marketed the drug under the name Procardia. Despite its initial commercial success, the drug faced a dosation problem: It was non-soluble and had to be taken three times a day. Realizing that if Adalat was to succeed in the long-term this problem had to be solved, Bayer invested heavily into its improvement. The R&D efforts finally led to a marginal dosation enhancement in that the drug now only had to be taken twice a day. New patents were obtained and drug sales continued. However, in the meantime a third party, the U.S. company Alza Corp., developed a technology that uses lasers to create holes in drug capsules to allow the relevant substances to be released in the appropriate place. Tests demonstrated that this technology could be used to reduce the dosage for Procardia to once a day. In 1989 Alza and Pfizer signed a worldwide exclusive licensing agreement for this OROS process technology, which Pfizer employed to create a superior product to Bayer's Adalat, accordingly called Procardia XL. In other words, through the aid of a third-party, Pfizer, as the licensee, was able to improve the licensed technology more effectively than the original licensor, Bayer.

The news quickly spread to Bayer itself, which obviously also wanted to benefit from this development. For some unknown reason it had failed to include a grant-back clause and therefore had to rely on its good business relationship with Pfizer and the fact that its worldwide patents could have prevented Pfizer from employing Alza's process outside of the U.S. The two companies therefore agreed that Bayer would obtain access to Alza's technology despite the lack of a grant-back. Due to these continued improvements, the sales of Adalat increased substantially and nearly two decades later it is still one of Bayer's five best selling products (*Bayer Annual Report* 2007).

Bayer has learned from this agreement and has since employed grant-backs whenever these could be negotiated. One of our interview partners therefore summarized that "Bayer then realized that grant-backs are very important to benefit from the innovative potential of one's licensees and their collaborators."

Insulin

Another example of licenses being used to innovate in an area critical to the health of many humans is the development of insulin. Diabetes, the chronic disease in which the body fails to create a sufficient amount of insulin, currently affects over 180 million people around the world. The World Health Organization further reports that around 5 percent of global deaths are attributable to the disease (WHO 2006). Fortunately, at least in the developed world, the treatment of diabetes has been considerably increased throughout the last century and with proper care patients can now live relatively normal lives.

After decades of research into the area, a group of Canadian researchers, largely from the University of Toronto, developed a process for extracting insulin from ox-pancreas that could be applied to the treatment of diabetes. They patented their treatment in the most important economies and in 1924 licensed five English companies to produce and commercialize insulin in all countries except Canada and the U.S. The Report on the Supply of Insulin (1952; p.12) clearly stated that "during the period 1928 to 1940 …[e]ach concern made technical progress and the quality of British insulin was generally improved." Substantial enhancements were made in terms of the insulin's purity and its formulation and manufacturing methods (Jewkes et al. 1969). Burroughs Wellcome for example started to use insulin in crystalline form in 1934. Two types of modified forms of insulin, Protamine Insulin and Protamine Zinc Insulin, which enabled a whole day's supply of insulin to be given in one injection, were introduced to the British market in 1936 and 1937, respectively (*Report on the Supply of Insulin* 1952).

In 1941 the British Insulin Manufacturers (BIM) association was formed in which the remaining four British insulin licensees collaborated to further improve insulin and to cope with the difficulties caused by World War II. In July 1949, the members of the BIM agreed "to the fullest possible extent and with the fullest exchange of technical information" to collaborate in "all aspects of research, development and production, assay (both chemical and biological) at all stages in the manufacture of insulin" (*Report on the Supply of Insulin* 1952; pp. 23-24). Any member who took out a patent was obliged to grant free licenses to the others. Giving information or granting licenses to non-members was only allowed with the full consent of the other members. Further improvements, such as the long lasting Globin insulin, were made during these years. *The Report on the Supply of Insulin* (1952; p. 29) even concluded that "we are impressed by the extent and thoroughness of the technical collaboration between the members of the BIM and by the increase in insulin yields which has resulted from it."

Computerized Dentistry

Just like pharmaceutical products, our society has become largely dependent on sophisticated medical devices. From syringes to pace-makers, from thermometers to breast implants—the range of products in this field is diverse and innovation therefore often requires expertise and equipment from a multitude of different realms, such as information technology, engineering, biology, physics, chemistry or material science (BMBF 2005). In a study of the changes in complexity, Allison and Lemley (2002) found that between the 1970s and the 1990s, there had been an increase of 238 percent in the amount of patents being cited per medical device patent, a higher increase than in any other field.

As noted above, user feedback can be of critical importance in the strive to develop innovative products. In the medical device industry, users have been especially active. Lüthje (2003) for example found that 22 percent of German surgeons had either developed a prototype or a marketable product. Shaw (1998) concurred: 53 percent of the 34 medical equipment innovations commercialized by British firms that he scrutinized were user-dominated. Benefiting from such sophisticated feedback and integrating innovative users into R&D processes therefore seems to be a promising strategy. Such market proximity also appears to be a reason why licensees are often in a good position to improve the underlying product or technology.

Therefore, we expected that licensees also frequently innovated in the medical device industry. Through in-depth interviews, we encountered a suitable example of a license transaction that was the basis of three subsequent generations of innovations in the dental industry. CEREC, short for ceramic reconstruction, is a CAD/CAM (Computer-Aided Design/ Manufacturing) technique that is slowly reshaping dental practice. The system enables dentists to design, manufacture and fit tailor-made ceramic restorations themselves without additional laboratory support (Wiedhahn 2006). The system can provide enormous service improvements to patients. As one dentist succinctly commented, "With the CEREC system, I can service my patient in just one visit that lasts a little over an hour" (Doyle 2000). Today well over 20,000 CEREC systems have been sold and the product division generates over $200 million per annum (*Sirona Annual Report* 2007, Reiss 2006).

The dental industry of the early 1980s was fragmented and consisted of numerous low-tech enterprises. The technological sophistication caused by computers had not yet reshaped the field. At the time Professor Werner Mörmann of the Dental School of the University of Zurich and Dr. Marco Brandestini, a befriended engineer, developed the idea of creating a computer-assisted design and manufacturing tool for the dental industry. After some extensive tinkering they patented their idea and decided to commercialize it with a corporate entity they called "Brains" (i.e. Brandestini Instruments). Within the following years a workable prototype was constructed and in 1985 the first patient was test-treated at the University of Zurich. Brains, with the intention of producing the device, originally bought materials to construct 25 machines and commenced to assemble these manually. Such basic form of production proved cumbersome, however, and their lack of marketing know-how as well as the limited availability of finances soon forced the two inventors to explore other options.

In their search for a partner who possessed global marketing expertise, the appropriate production capabilities and adequate financial means, they encountered the medical technology branch of Siemens. After nearly half a year of negotiations, the parties signed an exclusive worldwide license to the CEREC patents. The rights to further develop the technology remained with Brains, although Siemens was also granted the right to modify, amend and develop CEREC. Siemens marginally adapted the product to enable serial production and in 1987, within a year after the signing, introduced CEREC 1 to the market.

This initial commercial version of CEREC was designed to produce solid fillings such as cavities, called inlays. The original market success was very limited however, with only an estimated 250 machines having been sold annually between 1987-1994. While the product's idea was convincing as it enabled the dentist to produce inlays himself in one relatively short session for which he would otherwise need a laboratory that may take various days, its technical realization was inadequate. Dentists bought the machine because of its potential and not its inherent merits. This very early introduction however proved to be very smart in retrospect as it enabled Siemens to learn through commercialization. During this time it was able to collect an enormous amount of priceless technological and market information that served as a stepping stone for its future success. Brains, the licensor, soon realized that Siemens was much better suited to further improve CEREC and seized its own development. Professor Möhrmann became a long-term consultant who has since provided valuable know-how.

Siemens, as the licensee, subsequently used its experience with the technology as well as market feedback to develop an enhanced version. CEREC 2 was thus introduced in 1994. While its predecessor focused on side teeth, CEREC 2 could also handle front teeth and thus constituted a substantial improvement of the original device (Guinnessy 1997). While according to the former Siemens management team it still "under accomplished" user requirements, the device got much closer than its predecessor. With around 800 machines sold per annum it was an immediate market success.

During the next six years Siemens invested further substantial sums into CEREC's product development. In 1997 as part of the sale of Siemens' Dental Division, Sirona was formed which has since been responsible for CEREC. In 1999, after thirteen years of improving CEREC as a licensee, Sirona finally purchased the patents. Therefore every enhancement of CEREC that was made between the years 1986-1999 serves as an example of innovations made by a licensee. During this time period the key improvements for the third generation, CEREC 3, were made. This sophisticated Windows NT-based CAD/CAM system, introduced in 2000, therefore serves as the culmination of CEREC licensee innovation. While the first two versions could only produce single and dual-surface inlays, CEREC 3 could create multi-surface inlays, single onlays, veneers, and posterior and anterior crowns (Doyle 2000).

The market received the new product positively and studies have confirmed the high quality of the device. Pallesen & van Dijken (2000) for example, in an 8-year follow-up study, found that 84 percent of the inlays were estimated as optimal and 16 percent as acceptable. Reiss (2006) concurs with these findings. In 2003, a real-time 3D version of CEREC was introduced which in its current version according to the *British Dental Journal* (2008; p. 581) will allow the dentist "to produce probably the best ceramic restorations possible."

To summarize CEREC's development, the original license from Brains to Siemens resulted in a "whole family of products" or even in the birth "of a whole new industry" as Sirona's current CEO described it in an interview. The wide variety of CEREC-related products including the market-leading CAD/CAM products for laboratory products, CEREC inLab, and the large amounts of patents on the technology provide some further support for this view. Today, 32 percent of total company sales come from the CEREC portfolio (*Sirona Annual Report* 2007).

Akin to the Japanese success in becoming a technologically-based nation, a principal reason why Siemens/Sirona was able to improve the licensed-in technology was its sizeable investment into professionally organized CEREC-related R&D. It all started with Siemens' demonstration of commitment: a down-payment of around 3-4 times R&D costs plus royalties. Subsequently, in the period between 1986-1994 a commercialization team of 8-10 people worked on the development, with a further 15-25 million Deutsch Mark (≈ € 7.7-15.7 million) being invested into R&D. A well-organized CEREC research and development department was subsequently set up to work on the future of computerized dentistry.

The investments into license-related R&D were obviously also considerable in the examples of drug development and insulin. While to most people technological progress seems to happen inherently, the efforts required to make even minor improvements can be huge. Despite the current economic turbulences however, the thrust for technological improvements will remain strong. In light of the sharp, not always desirable, expected increase in the global population and the inevitable demographic ageing of the Western world, improvements in both drugs and medical devices, are of vital importance. Licenses seem to be useful collaborative tools to meet one of the global society's principal challenges. ■

CEREC History of Licensee Innovation

1980	Development of the CEREC method at the University of Zurich (Prof. Möhrmann, Dr. Brandestini).
1986	Improved workable prototypes. Further testing with patients at University of Zurich. Siemens acquires the exclusive license to market CEREC.
1991	Major improvement-introduction of an electronically controlled motor.
1994	CEREC 2 is introduced which can also be used to make onlays and veneers.
1997	Sirona is formed as the result of the sale of the Siemens' Dental Division.
1999	Sirona finally acquires the remaining CEREC patents and ceases to operate as a licensee.
2000	CEREC 3 is introduced. It is now a compact Windows-based CAD/CAM system.
2002	Milestone: over 2,500 CEREC users in the U.S. and over 5 million CEREC restorations placed worldwide.
2003	CEREC 3D is introduced.

Sources: Personal Interviews and Sirona (2007).

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