Technology transfer in pharmaceuticals

The case of an antibiotic in Japan

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This article demonstrates the roles of corporate strategy, organizational management, and national institutions in the process of technology transfer and commercialization in the pharmaceutical industry. A Japanese case study about the development of a cephalosporin antibiotic by Takeda Chemical Industries reveals that several factors have to work together to ensure success in technology transfer and commercialization in the biomedical area in a developing country.

Introduction

Cefotiam is an antibiotic synthesized and developed by Takeda Chemical Industries in Japan. This drug is classified in a sub-group of antibiotics called cephalosporins. Cephalosporins are analogues of cephalosporin C and have a similar chemical structure to penicillins: both subgroups of antibiotics possess the structure called β-lactam.

Takeda formed a research alliance with a Swiss company for cephalosporins. The company produced several imitative and commercially less successful cephalosporins, and eventually succeeded in the development of cefotiam. Cefotiam was synthesized in 1974 and launched in Japan in 1981. Cefotiam is classified as one of the so-called second-generation cephalosporins, which have a broader spectrum of activity than first-generation ones, but in general less antibacterial activity against gram-negative bacteria than third-generation ones.

However, this does not mean that second-generation cephalosporins became obsolete after the advent of third-generation ones. This is because doctors do not always use third-generation cephalosporins for fear of making bacteria resistant to antibiotics. In Japan, the increase of antibiotic-resistant bacteria has been a major medical problem since the 1980s. A narrower spectrum of activity has the advantage of preventing a broad range of bacteria from unnecessarily becoming antibiotic-resistant. Thus cefotiam has sold very well in Japan even after the advent of third-generation cepha-
Cephalosporins. Sales in Japan were estimated to be about ¥ 22 billion (about $200 million) in 1998.

This article aims to analyze a detailed Japanese case study to draw lessons that may have implications for international technology transfer in pharmaceuticals and other biotechnological products. The case study describes Takeda’s experience from the introduction of the basic technology of cephalosporin to the successful launch of its own new drug in the market. Although the case is not a very recent one, I believe that it is beneficial because it demonstrates the process of the absorption and the commercialization of advanced biotechnology when Japan was a developing country.

The case study is based on fieldwork conducted from 1998 to 2000. The data were obtained from various sources, including published materials, such as academic articles, review articles, works on the history of medicine, industrial and corporate histories, memoirs, and statistics, as well as interviews with key figures engaged in the development of the drug. The interview with Dr. Katsura Morita, who was the project manager, was conducted on 8 February 1999.

The interview with Dr. Mitsuo Numata, who succeeded him in the synthesis of cefotiam; Dr. Kenji Okonogi, who was involved in the biological study; and Mr. Nobuyoshi Hiramatsu, who was involved in the development of the drug; was conducted on 26 January 1999. Complementary investigations by email or postal mail with them were also conducted after the interviews. In this article, only a few sources are cited due to space limitations. For the full story and the complete list of references, please refer to my book.

The book also includes several other case studies of innovation in the pharmaceutical industry in Japan.

**Discovery and early progress of cephalosporins**

In 1945, Giuseppe Brotsu, a professor at the Institute of Hygiene in Cagliari, Italy, sampled sea water near a local sewage outfall and discovered a species of mould, *Cephalosporium acremonium*, which produced a substance with a wider antibacterial activity than penicillin. In 1948, he sent a sample to Sir Howard Florey in Oxford, who took up further investigation. By 1953, Edward Abraham and his colleagues at Oxford found a new antibiotic, named cephalosporin C, which had some unique properties, such as non-toxicity, stability and, in particular, resistance to penicillinase, a class of enzymes produced by bacteria. These enzymes destroy penicillin, the most widely used antibiotic at the time. The researchers found that cephalosporin could become the very successor of penicillin.

The production of cephalosporin C in quantity was difficult at the time. The Oxford researchers helped the Medical Research Council’s Antibiotic Research Station to produce the substance on a larger scale. The National Research Development Corporation (NRDC) secured patents related to the production of cephalosporin C. The Antibiotic Research Station and NRDC had been founded to exploit discoveries made in Britain, which had not been achieved in the case of penicillin. In 1956, NRDC began to organize meetings between Glaxo, the researchers at Oxford and the Antibiotic Research Station. By 1957, 100 mg of cephalosporin had been produced by Glaxo, contributing to the work to confirm the chemical structure of the substance.

Several foreign companies contacted NRDC and signed licensing agreements with the corporation related to cephalosporin C: Squibb and Eli Lilly in the USA in 1959; Merck, Pfizer, SmithKline & French (all in the USA), Ciba (Switzerland), Farmitalia (Italy) in 1960; and Fujisawa in Japan in 1961. However, the possibility of developing cephalosporin C itself as a drug in practice disappeared when mexiticillin, a potent semi-synthetic penicillin, showed resistance to penicillinase in 1960. By 1960, the researchers at Oxford had identified the chemical structure of cephalosporin C, and found that 7-aminocephalosporanic acid (7-ACA) was a rich source of semi-synthetic cephalosporins that had much higher potency than cephalosporin C. The critical problem in exploiting the commercial potential of cephalosporins was to discover a method for producing 7-ACA on a large scale.

In 1960, Robert Morin and his colleagues at the Lilly Research Laboratories devised a more efficient procedure for converting cephalosporin C into 7-ACA. By that time, both Eli Lilly and Glaxo had achieved large-scale production of cephalosporin C by fermentation. Thus, 7-ACA became available in larger quantities, and a number of derivatives were synthesized and examined in the search for potent antibiotics. At Eli Lilly, Robert Chauvette and his colleagues prepared a series of 7-ACA derivatives, and cephalothin was selected for clinical trials from them. This was marketed in 1964, becoming the first marketed cephalosporin. Shortly after that, Glaxo also succeeded in making a marketable semi-synthetic cephalosporin, cephaloridine, which was marketed in 1964. Both cephalothin and cephaloridine were claimed to have a broader spectrum of activity than penicillins, to be active against some penicillin-resistant bacteria, and to be free from serious side effects. Safety for patients with penicillin allergy was also reported. Eli Lilly then synthesized the first orally active cephalosporin, cephalexin. Shortly after, however, this drug was replaced by a better-absorbed oral cephalosporin named cephalexin, which was synthesized independently by Eli Lilly and Glaxo and marketed in 1967.

In 1970, Chauvette and his colleagues at Eli Lilly developed a new chemical process for converting penicillin into cephalexin. This production process could be applied to other cephalosporins, and made the production of 7-ACA more efficient. By 1971, several cephalosporins with similar properties became clinically available, including cefazolin (Fujisawa), cephalorin (Bristol), and cephacetrile (Ciba-Geigy). These cephalosporins were later called first-generation cephalosporins; they were more active against gram-positive bacteria such as staphylococci and streptococci (non-resistant ones), but less active against gram-negative bacteria such as *E. coli*, *Klebsiella* and *P. mirabilis* than second-generation cephalosporins such
as cefamandol, cefaclor (both were developed by Eli Lilly) and cefuroxime (Glaxo), which had been marketed since around 1972. When Takeda started research on cephalosporins in 1970, first-generation cephalosporins were their exemplars and the targets to be superseded.

**Research on cephalosporin**

Takeda Chemical Industries is one of the oldest pharmaceutical companies in Japan, and also has decades of history of pharmaceutical research, including prodrugs of vitamin B1 (Arinamin®) which were major products of the company for a long time. In the 1960s and 1970s, antibiotics became the leading drugs that brought substantial profits into pharmaceutical companies in Japan. In this area, however, Takeda had no competitive products until the end of the 1960s.

In 1967, Takeda started research on semi-synthetic penicillin and succeeded in synthesizing sulbenicillin disodium by 1968, which was marketed in 1973 (Lilacin®). The company also started preliminary research on cephalosporins in 1967. In order to discover a new cephalosporin, however, they had to establish the supply of 7-ACA, which was not generally available. In November 1970, Takeda agreed with Ciba-Geigy to cooperate on cephalosporin research. Under this agreement, in 1971, Takeda started intensive research on cephalosporins with 7-ACA supplied by Ciba-Geigy. Results of the research would be shared between both companies. Takeda also started research on production of cephalosporin C in 1970. This research resulted in the invention of a new production process for deacetylcephalosporin C (DCPC) in 1973, which was later found could be used as an alternative material for production of cephalosporins. The sales force of Takeda, however, could not just wait for the birth of their new cephalosporin. Immediately after the agreement with Ciba-Geigy, the company developed a new production process for cephalaxin, and marketed its generic product in 1973 under the process patent system in Japan. In addition, Takeda and Ciba-Geigy cooperated on clinical trials and marketing of Ciba’s cephalosporin and cepheactrile in Japan. This was marketed in Japan in 1978.

The earliest attempt at synthesizing a new cephalosporin at Takeda was conducted by the same research group that had created sulbenicillin disodium, a semi-synthetic penicillin. In May 1970, they began to synthesize new cephalosporins on a small scale. They found that one of them, SCE-20, which had the same side chain as sulbenicillin disodium, had an activity against a particular group of gram-negative bacteria called *Pseudomonas aeruginosa*. This interested the researchers because existing antibiotics were largely ineffective against these bacteria. In 1971, with a supply of 7-ACA from Ciba-Geigy, they synthesized further analogues of SCE-20, and found that two of them, SCE-120 and SCE-129, were much more active against the bacteria than SCE-20 though they were not very active against other bacteria. Although there was doubt about its marketability, Takeda decided to develop SCE-129 in 1973 because of its unique activity against *Pseudomonas aeruginosa*. Researchers at Ciba-Geigy and academic specialists in infectious disease supported Takeda’s decision. SCE-129 was named cefsulodin and launched in 1981 (Takesuldin®). From the beginning, however, it was obvious that this would not cover the requirements of the sales division of the company, because of the drug’s narrow range of antibacterial activity. They needed a cephalosporin with a much broader range. Although these early attempts did not earn much income, it should be noted that they earned trust from Ciba-Geigy and ensured a further supply of 7-ACA, which helped further cephalosporin research at Takeda. The research group that produced cefsulodin did not belong to the Central Research Division, but to the Manufacturing Division. They were somewhat peripheral as researchers in Takeda (Numata interview). The search for a broader cephalosporin, which the company truly needed, was conducted by the ‘mainstream’ of Takeda’s research division.9

**Discovery of cefotiam**

Takeda charged the First Chemical Research Department at the Central Research Division led by Katsura Morita with research to discover a new cephalosporin in 1971. Morita described this project as ‘a life-betting gamble’ for the company and for himself. The project was created by the strategic needs of the company, and the project team had to achieve the goal though they had no experience in synthesizing cephalosporins. If they failed, they would have to take responsibility for the failure, and the company would have lost out in the Japanese antibiotic market. Two of the staff of the Investigation Department also participated in the project team. They investigated almost all related patents and literature, and mapped the situation of cephalosporin research in the world, including chemical structures and antibacterial properties of all cephalosporins available. There were pessimistic opinions expressed by the team, when they looked at the chart. He had to persuade his team members.

I said, ‘There were only several thousand compounds. Despite this, no existing cephalosporin had stronger activity [against gram-positive bacteria] than penicillins. In addition, penicillins were cheaper than cephalosporins. So, we can catch up [with leading companies]. Moreover, penicillin has only one place to be modified. But cephalosporin has two places. That means hundreds of thousands of compounds in principle can be synthesized. Not the level of several thousand. So, we have a chance.’ (Interview)

He succeeded in his persuasion. Morita also faced the question of which approach to adopt: random searching or rational searching. He thought about his available resources and chose the latter. This is how he put it:

The question was which was better: to make as many compounds as possible without thinking until coming across a hit, like blind shooting; or to make a working hypothesis first, then begin to synthesize compounds based...
on the hypothesis. I was afraid we would not tolerate the former choice. I thought we should make a hypothesis about why cephalosporins were active, what kind of mechanism killed bacteria, and what structure should be designed. The hypothesis had to be unique, something that others did not share. I thought we should make such a hypothesis by ourselves. My staff agreed with me. (Interview)

The hypothesis was made on the basis of the (organic) chemistry of the related area and an investigation into the structure-activity relationship of existing cephalosporins. Morita and his colleagues conjectured that an ‘active hydrogen’ in the side chain of a cephalosporin molecule was linked with antibacterial activity of the drug by enhancing the chemical reactivity of the molecule to the cell-wall-making enzyme of bacteria. 7, 10 Not all team members were convinced that they could work with it. Based on this hypothesis, they considered putting a particular atomic group called β-ketoacid into the side chain in order to produce an ‘active hydrogen’. This structure was chosen because it was unique and not protected by patents of other companies (Numata interview). However, it was clear that this was a hard task because β-ketoacid was very unstable. 7

Morita thought that this project should be completed in at most three years; and he organized five dedicated research groups. This was an exceptionally concentrated deployment of a research force. Three of the groups were charged with chemical synthesis; the other one was in charge of the supply of β-ketoacids (Morita interview; Numata interview). Morita mixed ‘lay researchers’, that is, researchers who were not specialized in the area, into the research groups. As he put it, ‘Cephalosporins are more expensive than penicillins.’ ‘Cephalosporins are less active than penicillins.’ People who were familiar with antibiotics and penicillins tended to say such words to me. I did not want those people in my project team. I preferred ignorant people without such prejudices. Ignorant people can act boldly, take drastic measures and find something unexpected. … Indeed, eventually, they did produce excellent results. (Interview)

Mitsuo Numata, the leader of the winning research group in this project, was one of the ‘lay researchers’. He shared Morita’s opinion:

[A success point is] that [Morita] did not use specialists only, but mixed lay people with specialists… If the team members had been specialists only, their view would have been much narrower. The team needed someone with foolishness enough to challenge what specialists believed to be impossible. Of course, lay people only would not have produced any better results. Mixing was important. (Interview)

There was keen competition between the research groups. Numata, one of the group leaders, and Kenji Okonogi, who conducted the biological study of the compounds synthesized by all research groups, described the situation at that time lightheartedly: HARA: Was there exchange of information between the research groups? NUMATA: No. Rarely. Because we were fighting each other [laughs]. Members of each group spoke ill of other groups at Okonogi’s laboratory. He was a good listener.

OKONOGI: Yes. I can confess it now. To be honest, it was a very hard job to be fair to every group [laughs].

NUMATA: I asked him, for example, not to give this information to Dr Ochiai [laughs]. All of us had a strong sense of rivalry. However, Morita had the ability to control this situation. (Interview)

Morita made careful efforts to control conflicts inside his research organization. He described an example of his efforts:

I did not become a co-author of papers produced by the researchers in my department after I became the Head. I even declined to be mentioned in acknowledgements… If I had allowed them to put my name into their papers, I could not have promoted competition in my organization. If I had become a co-author of one research group, I would have had to become a co-author of another research group, in order to be neutral between them. But if I had done this, it would have made me look indifferent and somewhat irresponsible. (Interview)

In the first year of the project, SCE-150, which did not include β-ketoacids in its structure, was synthesized by one of the research groups. Although SCE-150 was as potent as the most potent cephalosporin available at that time, Morita gave up its development because he believed that it would become obsolete before it appeared on the market several years later (Morita interview).

The research group led by Numata succeeded in putting β-ketoacids into cephalosporin molecules and synthesized many compounds. Most of them showed only disappointing activity. However, when they introduced an atom group called methyl-thio-methyl to the β-ketoacids side chain, the resultant compound showed fairly high potency. 10 This result encouraged them to make further analogues of this compound. Serendipitous discovery occurred in the process: when they tried to combine another related atom group called thiocyanate with the side chain, the nuclear magnetic resonance analyzer in their laboratories was broken; because of this, the compound was left for a week. After the machine was repaired, a young researcher of the group analyzed the compound and found that it was different from what they expected.

They examined the unknown compound and found that the atomic group at the end of the side chain had become a cyclic structure. Moreover, this new compound possessed remarkable antibacterial activity, stronger than that of any existing cephalosporin, particularly against gram-negative bacteria. They then made an effort to optimize the molecule. The consequent cephalosporin, codenamed SCE-785, satisfied the requirements for a competitive cephalosporin in future market. Takeda decided to develop SCE-785 in July 1974, five months after its synthesis. 10, 9 The unique structure of SCE-785 became a standard component structure: most third-generation cephalosporins developed later adopted it. 9
SCE-785 was pre-clinically tested for about a year and its efficacy was confirmed. However, tiny deposits were observed in the kidneys and the bladders of rabbits to which a lot of SCE-785 had been administered. This was believed to be due to the low solubility of the compound in water. Morita insisted on continuing its development because results in humans might be different from those in rabbits, but toxicologists at Takeda argued that they should wait for a better drug (Morita interview).\(^7\) SCE-785 proceeded to clinical trials with healthy volunteers, but one of them showed side effects. This was also believed to be due to the low solubility of the compound in water (Numata interview). The development of SCE-785 was stopped in December 1975.\(^8\)

Along with the development of SCE-785, the search for a better cephalosporin was continued in Morita’s department. This time, Morita concentrated researchers’ efforts on making better analogues of SCE-785 (Morita interview).\(^7\) At this stage, he made Numata’s group open up their information to other researchers in order to promote competition among them (Morita interview). Okonogi, who was involved in assaying these compounds, described how busy he was at that time, dealing with the compounds which were synthesized one after another:

We examined about 30 compounds a week. We divided them into two sessions. It took three days to assay compounds - plant bacteria on the first day; put compounds into the culture the next day; and then observe results on the third day. By that time, our company had adopted a five-day working week. ... So we had two sessions: Monday to Wednesday and Wednesday to Friday. We continued this for weeks. (Interview)

As a result, 154 compounds were synthesized. When the development of SCE-785 was stopped, several compounds that had higher solubility in water were chosen from the newly synthesized compounds. After detailed examination of these compounds, in December 1975, Takeda decided to develop one of them, SCE-963, in place of SCE-785. This compound, named cefotiam, also had a broad range of activity and was in particular more active against some gram-negative bacteria than existing antibiotics at that time. Cefotiam quickly passed pre-clinical tests and proceeded into clinical trials in August 1976.\(^5\)

Development of cefotiam

The development of an efficient production process for cephalosporins proceeded concurrently with chemical syntheses and biological studies of the compounds.\(^9\) Production costs of cephalosporins had been a critical problem for the commercialization of the drugs. Penicillins were much cheaper than cephalosporins at that time, and this produced obstacles to research and development of cephalosporins. Morita faced such criticism when he led the cephalosporin project at Takeda.

As he put it: One of my senior colleagues asked me, ‘Morita, I hear you have begun to research cephalosporins. But do you know the prices of penicillins and cephalosporins?’ I said, ‘I don’t know exactly, but cephalosporins seem expensive.’ He said, ‘Ten times as expensive. I mean, costs of raw materials. In addition, penicillins are fast in fermentation. Moreover, it is easy to extract penicillins into butanol, but cephalosporins are hydrophilic and insoluble in butanol. How could you possibly succeed?’ (Interview)

Takeda had made efforts early on in their research to reduce the costs of cephalosporins. As I mentioned above, they developed a new production process of deacetylcephalosporin C (DCPC) in 1973. They then invented a new route to produce semi-synthetic cephalosporins such as cefotiam from DCPC in good yields and on a large scale; this reduced production costs to an acceptable level.\(^9\) It should be noted, however, that this problem of the cost of cephalosporins was also related to patents secured by other companies.

Numata explained: At that time, only members of the syndicate [organized by NRDC] could use [the raw material, 7-ACA]. ... When we thought about methods of its production, we found more patents protected them. So, only DCPC enabled us to circumvent those patents. ... So, we at first made DCPC and used it as the raw material of cephalosporins. Later, those patents expired one by one, and it became more economical to use 7-ACA available on the market than to use DCPC made by us. (Interview)

Takeda also had to design a unique preparation to make cefotiam suitable for practical use. Because of the production route of cefotiam and in order to maintain stability of the compound, the company decided to market cefotiam as a salt with two moles of hydrochloric acid. When this salt alone was dissolved in water, however, the solution was too acidic to be appropriate for clinical use. Therefore, they prepared sodium carbonate with the drug to neutralize the acid. Then, they reduced the pressure in the phials containing the preparation to control the carbon dioxide generated when water was added to them. To produce the phial, they also had to develop new equipment for packaging.\(^3\) Fortunately for them, however, the good solubility of the prescription was highly appreciated by medical practitioners including doctors and nurses. (Hiramatsu interview) This is because medical practitioners often face cases in which they have to administer an antibiotic to patients immediately. (Numata personal communication, June 2000)

Clinical trials of cefotiam went ahead smoothly. In February 1977, it proceeded to Phase II. Its double-blind trials with cefazolin, a highly potent first-generation cephalosporin developed in Japan, were conducted from November 1977. The results of these Phase III trials were presented at the annual conference of the Japan Society of Chemotherapy in June 1978. The efficacy and safety of cefotiam were supported there. Based on these data, Takeda and its development partner Ciba-Geigy (Japan) obtained approval from the Ministry of Health and Welfare in 1980 for manufacturing cefotiam. Takeda launched cefotiam under the trade name Pansporin® in February 1981.\(^8\) Cefotiam was also marketed in several foreign countries including Germany, but its sales abroad were limited.
Two institutional factors contributed to the relatively rapid development of cefotiam in Japan. First, because antibiotics were used to cure acute diseases, its long-term side effects were regarded as less important than those of drugs for chronic diseases, such as hypertension and hypercholesterolemia. In fact, the regulatory body was keen to approve any better antibiotic as soon as possible. Second, there was a well-organized society of specialist doctors in the chemotherapy area in Japan, the Japan Society of Chemotherapy. This society had its own routine for managing clinical trials. When pharmaceutical companies asked the society to undertake clinical trials, it organized and arranged them; then, they proceeded steadily under the initiative of the society. This system strongly promoted the development of antibiotics in Japan. [Hiramatsu interview]

Implications

The case study above includes several lessons for the absorption and commercialization of biomedical technology. First, technology transfer is not only a matter of technology but also a matter of strategy, organization, management and national institutions.

Second, from a strategic point of view, targets should be made visible. This means that the target should be well defined and shared by the people involved. If the target is clear, people in the organization can focus on it easily. In this case, cephalosporins were expected to be the successor of penicillins, the best selling antibiotics at the time. Although people anticipated several obstacles to get hold of the technology, the challenge was regarded as rewarding. Because the technology was fairly mature (about 17 years had already passed since the discovery of cephalosporin C, when Takeda began their research on cephalosporins), the company could learn a lot from the experience of existing cephalosporins. Existing drugs also worked as benchmarks.

Third, a step-by-step approach is appropriate for mastering new technology. In this case, Takeda at first produced and sold a generic cephalosporin, then it developed a new cephalosporin for a niche, and finally it launched a new cephalosporin towards a general market. This incremental approach seems to have several merits: (a) it utilizes learning fully; (b) it reduces the risk of failure; (c) it secures the trust of business partners; and (d) it maintains and improves complementary assets such as manufacturing ability and sales force.

Fourth, the management of the organizational process is very important. There are differences and conflicts within a company. In this case, Morita carefully managed his research groups to ensure both competition and collaboration between them. He also managed to overcome resistance within his organization. Without his effort and top management’s support, the project might not have survived.

Fifth, commercialization requires deep consideration for customers and competitors. For example, Takeda’s efforts to develop a new production route for cost reduction and to adjust drug preparation for practical convenience are noteworthy.

Finally, national institutions are important for the commercialization of new technology. In this case, the cooperative attitude of the regulatory office and medical society was the key to the smooth launch of cefotiam. The favorable institutional settings for antibiotics development in Japan, indeed, turned the country into one of the largest producers and consumers of antibiotics.

These lessons might be useful for technology transfer not only in the biomedical sector but also in other sectors. I hope that readers will find further implications from this case study based on their own interests.

References