

Scale Expansion and the Change of Research and Development Activities — Case of Takeda Pharmaceutical Company —

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Abstract

In pharmaceutical companies, research and development (R&D) activities to create new drugs, which may become a resource for competitive advantage, is one of the most important corporate activities. These R&D activities change along with the expansion of the corporate scale. Thus in this article, by reviewing the case of Takeda Pharmaceutical Company which rapidly expanded its scale during the 1990's as an example, we could show that the along with the expansion of the corporate scale, R&D activities change from research-focused activities to development-focused activities.

By dividing R&D of pharmaceutical companies into the research process and the development process, and analyzing each process in detail, we could observe that while the scale does not affect the research process output, it does affect the development process output. We then analyzed the case of Takeda Pharmaceutical Company and could see that its R&D activities changed from research-focused activities to development-focused activities along with its scale expansion.

Keywords: *scale expansion, research and development activities, change, Takeda pharmaceutical company*

1. Introduction

The 21st Century is the century of life science, and the pharmaceutical industry is central in the life science industry. For pharmaceutical companies taking an active part of such industry, it is said that the research and development (abbreviated as R&D) activities to create new drugs which may become a resource for competitive advantage, is one of the most important corporate activities.

Let's explain it this way: First, it has been pointed out that the resource for competitive advantage is the internal resources of a corporation (Barney, 1986, 1991, 2001; Collis and Montgomery, 1998; Nelson, 1991; Rumelt, 1984; Wernerfelt, 1984). If this theory is applied to the pharmaceutical industry, such internal resources are the above-mentioned new drugs. In addition, many studies have pointed out that the capability to generate such internal resources is the resource for the continuing competitive advantage. (Hamel and Prahalad, 1994; Helfat and Peteraff, 2003; Nonaka and Takechi, 1995; Teece et al., 1997; Zott, 2003). Therefore, R&D activities to generate new products, as it may be the resource of a continuing competitive advantage, should be the most important corporate activity in the field of the corporate strategy.

In empirical studies on the automotive industry by Clark and Fujimoto(1991), the computer

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industries by Eisenhardt and Tabrizi(1995), and, the disc drive industry by Christensen(1997), the software industry by Iansiti and MacCormack(1997), and the material industry by Utterback(1994), the R&D strategy of companies of these various industries are shown.

In addition, R&D activities to create new drugs should be the most important corporate activity as it may be the resource of a continuing competitive advantage of each pharmaceutical company. (Kuwashima, 2003)

The R&D activities of a pharmaceutical company changes as the scale of the company expands. Thus in this article, we verified that the R&D activities of a pharmaceutical company changes from research-focused activities to development-focused activities, using Japan's largest pharmaceutical corporation, Takeda Pharmaceutical Company (abbreviated as Takeda) as an example.

This article is organized as follows: In Section 2, by dividing R&D of the pharmaceutical companies into the research process and the development process, we describe that the scale of pharmaceutical companies does not affect the research process but positively affects the development process. In Section 3, we verify that R&D activities of the example Takeda, which rapidly increased its scale since the 1990's, changed from research-focused activities to development-focused activities.

2. Research and Development Processes of Drug

In this section, we will divide R&D of a pharmaceutical company into the research process and the development process, explaining that the determinant factors of the latter are different from those of the former.

In empirical studies on the automotive industry by Clark and Fujimoto(1991), the computer industries by Eisenhardt and Tabrizi(1995), and, the disc drive industry by Christensen(1997), the software industry by Iansiti and MacCormack(1997), and the material industry by Utterback(1994), the R&D processes of these various industries are shown. The R&D processes in companies of these industries are too intricately connected to simply divide the research process and development process. On the contrary, the pharmaceutical industry is characterized as being able to divide R&D into the two processes of research and development.

In this section, we will give an overview and describe the characteristics of these two processes and how different factors may affect the result. The R&D processes of a drug are shown in Figure 1.

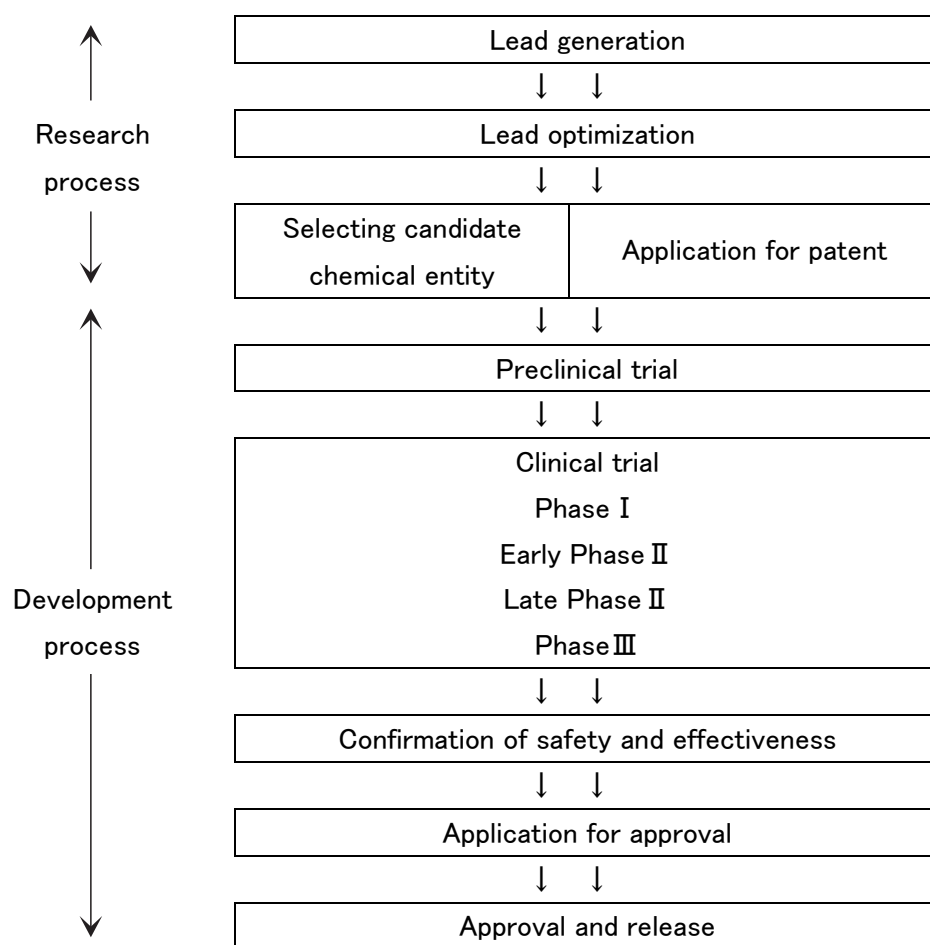


Figure 1: Research and Development Processes of a Drug

2.1 Overview and Characteristics of Research Process

The research process is the process to determine a new chemical entity (abbreviated as NCE) candidate for development. This process goes from the lead generation, to lead optimization, to the selection of a NCE that may become a candidate for development.

The lead generation is the activity to determine the active substance from a natural product or biologically active substance, whose effect is not strong but is unique and has potential, and is called the lead entity.

The lead optimization is the activity to conduct chemical modification based on the generated lead compound. Efforts to enhance the effect and alleviate the toxicity, as well as to find a NCE with superior effectiveness, safety and ADME (absorption, distribution, metabolism and excretion)

are made. Next, the optimized NCE is determined to be a candidate for development and application for a substance patent is filed. Furthermore, any related patents such as the manufacturing process of the NCE shall also be filed in turn. Thus a NCE and a pharmaceutical patent result from the research process.

The research process that generates such a result has the following characteristics: Regarding the lead optimization, with the appearance of the combination chemistry, the number of the synthetic compounds has dramatically increased. In addition, with the appearance of high-throughput screening where screening is conducted quickly, many NCEs covering a broad range for various therapeutic purposes have emerged. As a result, a large number of NCEs have been generated and optimized compounds have been obtained in a short time. Therefore, within the research process, lead optimization requires the introduction of the latest facilities, such as combination chemistry or high-throughput screening. However, investments for these facilities are much more inexpensive than those in the development process, which will be described later. Further, lead generation may be caused by serendipity even today, and even with an excellent facility for lead optimization, such facility may not be available without a lead generation. Therefore, throughout the research process, the result often depends on serendipity, so a large investment such as that seen in the development process, is not required.

2.2 Overview and Characteristics of Development Process

The development process takes the NCE obtained from the research process and develops it into product to be used in medical supplies. This process goes from the preclinical trial to the clinical trial, and then to the approval and release. While the preclinical trial is conducted on animals, the clinical trial is conducted on humans.

To ensure the safety and effectiveness of the NCE, trials are conducted on animals such as rats, dogs or monkeys rather than humans during the preclinical trial.

During the clinical trial, trials using an NCE that has passed the preclinical trial are conducted on humans. The clinical trial is divided into the following three steps; Phase I, Phase II and Phase III as steps up to application for approval.

During Phase I, trials regarding the safety of a NCE are conducted on healthy individuals. During Early Phase II, trials regarding the safety and effectiveness, and ADME of the NCE are conducted on a small number of patients. During Late Phase II, the safety and effectiveness is confirmed over a broader category of patients as well as determining the method of treatment and dosage by clarifying the medicinal benefits and the diseases affected by the NCE. During Phase III, the safety and effectiveness, the method of treatment and dosage conducive to the appropriate disease, side effects and drug interaction are verified. Application for approval will be made based on the data obtained through these processes and the NCE whose safety and effectiveness is recognized, shall be approved by each country as a medicinal product for the appropriate disease. Therefore, a new drug that approved is considered the result of the development process.

The development process which generates these results has the following characteristics; in principle, the clinical trial must be conducted in all countries where such medicinal product is expected to be supplied, and the medicinal product must be approved as a pharmaceutical product by each country based on the data obtained from that clinical trial.

Since 1991, the international harmonization of standards for the approval process of pharmaceutical products between the U.S., the E.U. and Japan has made progress due to the ICH (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use). Nonetheless, clinical trials have not been harmonized completely. Thus a large amount of development investment and many large organized activities are still required in the development process at present. Even if part of a clinical trial is exempted by virtue of the harmonization, the development investment and organized activities required for a clinical trial are nonetheless huge.

Therefore, during the development process, especially at the stage of the clinical trial, a vast amount of development investment and many large organized activities are required. In particular, locally incorporated companies must be established in the countries where the medicinal product is to be supplied and clinical trials with a large amount of the development investment must be conducted.

2.3 Effect of Scale on Research Output and Development Output

In this regard, JPMA (2006) reported the following characteristics; success rate at each research process and development process are 0.05% and 20%, respectively; 20-25% of the R&D investment is used for the research process and the remaining 75-80% is used for the development process. In addition, according to Kuwashima and Takahashi (2001), the main characters involved in the problem solving of these two processes are different: In the research process, it is the researcher, and in the development process, it is the pharmaceutical company itself. That is to say generally, during the development process, multiple teams or sectors within the company cooperate together in various activities, and a decision maker in a superior position solves the problem by coordinating with the company.

Many previous empirical studies observed that the scale of pharmaceutical companies does not affect the outcome of the research process (Comanor,1965; Gambardella,1992; Graves and Langowitz,1993; Henderson and Cockburn,1996; Jensen,1987; Odagiri and Murakami,1992; Vernon and Gusen,1974). Among these, only studies conducted by Schwartzman(1976) concluded that scale affects the output of the research process.

On the other hand, regarding the development process, studies conducted by Cockburn and Henderson (2001) suggested that the scale of pharmaceutical companies may affect the output of the development process.

Actual data and previous empirical studies also show that while the research process does not require a large amount of research investment or organized activities, the development process does.

Therefore, the R&D activities of a pharmaceutical company will be supposed to change as the scale of the company expands.

3. Case Study of Takeda Pharmaceutical Company

From the discussion in the previous section, it may be assumed that R&D activities will change from research-focused activities to development-focused activities as the scale of a pharmaceutical company expands.

In the 1990's, Takeda, one of the largest pharmaceutical companies of Japan, started to proactively expand its business overseas, such as in U.S. and E.U.. By this, Takeda established high position in U.S. and E.U., and its sales increase in such overseas markets became the key factor for its dramatic scale expansion.

Now, we will verify the fact that as the scale of Takeda expanded, the R&D activities changed from research-focused activities to development-focused activities, based on the following 3 points;

First, it could be shown that the R&D activities will change from research-focused activities to development-focused activities based on the remarks made by the corporate managers.

Takeda Presidents, Kunio Takeda and Yasuchika Hasegawa, have tried to strengthen their research capability, but, throughout the research process, the result often depends on serendipity as above.

Kunio Takeda, who became company president in 1993, consistently pursued R&D activities focusing on research throughout the 1990's and maintained such a policy in 2000. However, he began changing focus of R&D activities to development in 2001. He spoke that "we aspire to grow with self-owned research and development in the years to come" in 2000, but he spoke "we need to introduce research output for the development." in 2001. By the time Yasuchika Hasegawa became president in 2003, it was common knowledge that R&D activities had changed to development-focused activities (Table 1).

For reference, Table 2 shows the new drugs released internationally by Takeda during the 1990's. Since all the drugs were researched by Takeda, it can be said that the R&D activities of Takeda were research-focused activities. For instance, Leuplin and Prevacid were researched by Takeda, but were developed other company in U.S..

Second, it could be shown that there were specific policies to introduce research output. Takeda added introducing research output to self-owned research. This occurred because R&D activities changed to development-focused R&D.

In 2003, after direction of the development-focused R&D activities became clear, a system to introduce research output was established. Specifically, a system that investigated research output from an outside company, and a company structure that introduced such research output, was established. Then after 2005, the actual introduction of research output began (Table 3).

Third, it could be shown that actual cases where development-focused R&D activities were conducted, introducing research output.

In 2001, the initial year that R&D activities changed to development-focused activities, Takeda conducted development, introducing the research output from Mitsubishi Pharma. It seems

Table 1: Contents of Remarks Made by Takeda Management

Year	Speaker	Contents
2000	President Kunio Takeda	During the 1990's, our company grew due to big sales new drugs whose research and development were conducted by our company. We aspire to grow with self-owned research and development in the years to come.
2001	President Kunio Takeda	Under the 5-year Plan from 2002, we are attempting to establish a framework where we can release at least 3 international strategic products. Therefore, we need to introduce research output for the development.
2003	President Yasuchika Hasegawa	Because research and development capacities are essential to a pharmaceutical company, we are engaged in efforts to make research and development more efficient. But there are few candidates for the development. Thus we will radically change the existing method of research. In addition, we will use our financial assets to purchase development candidates from other companies.
2004	Chairman Kunio Takeda	While maintaining our independence, purchasing a company with big sales new drugs is worthwhile.
2004	President Yasuchika Hasegawa	In order to survive in the world market, big sales new drugs are indispensable. Thus we will strengthen our research capability. Since searching for a truly desirable candidate for new drug development takes time, we will consider an acquisition if such a candidate for new drug development appears. However, this is only a complement to our self-research efforts.
2005	President Yasuchika Hasegawa	At last, the effect of the strengthening measure regarding the candidate for development began to appear. In the future, we will proactively obtain licenses for candidates for development from outside the company when our research can not provide enough candidates for development.
2006	President Yasuchika Hasegawa	Patents of big sales new drugs, which have been driving our expansion of business performance since the latter half of 1990's, will begin to be expire from 2009. There are not enough candidates for development to enhance corporate growth, while absorbing yield decrease due to patent expiration. Despite the importance of in-house research, in-house research does not meet the time limits. Thus in the short term, licensing from an outside source is unavoidable. Because it takes a long time before a new drug may contribute to business performance, we will obtain the licenses with priority to candidates for development that already have entered into the later development stage. It is desirable to be able to purchase the development license for a candidate of a new drug, but if that is not possible, we will engage in corporate acquisition.
2006	Chairman Kunio Takeda	Nevertheless, while we may purchase candidates for development from outside sources, it would be disadvantageous if we were not able to continue our own research for development candidates. We shall be wary of the decrease of research capability, avoiding a slack way of thinking that it is sufficient to buy a development candidate because we have the financial assets.

Source: This Table was compiled from Nihon Keizai Shimbun.

Notes: This Table shows every news published in Nihon Keizai Shimbun since 2000.

Table 2: New Drugs Released by Takeda during the 1990's

Brand name	Generic name	Birth year	Development in Japan		Development in US		Development in EU	
			Year	Company	Year	Company	Year	Company
Leuplin	leuproreline	1980	1992	Takeda	1985	TAP	1989	Takeda
Prevacid	lansoprazole	1986	1991	Takeda	1995	TAP	1991	Takeda,GSK,Aventis
Actos	pioglitazone	1986	1999	Takeda	1999	Takeda	2000	Takeda
Blopress	candesartan	1991	1999	Takeda	1998	Takeda,AstraZeneca	1997	Takeda,AstraZeneca

Source: This Table was compiled from Documents by Takeda Pharmaceutical Company.

Notes:TAP is joint company of Takeda and Abbott.

Table 3: Specific Policy for the Introduction of Research Output

Year	Specific Policy
2003	We have obtained the right to provision by the U.S. biotechnology consultant, Drug Development, with detailed information on NCEs, which are subject to research by each company. This is to investigate which NCEs should be introduced.
2003	The Medical License Department has been established in our company. This is aimed to extensively introduce NCEs from other companies.
2005	We purchased the U.S. bio-venture, Syrrx, which has NCEs for the treatment of cancer and diabetes.
2005	We have bought back the development and distribution rights for drugs used to treat diabetes, which the acquired company Syrrx had provided to other companies.
2006	The number of participants from other sections in the company to the Business Development Department that obtains new drugs under development by other companies exceeded 20 persons.
2006	We obtained from the Canadian bio-venture, Arius Research, and the rights to develop NCEs owned by the said company, for the next 3 years.
2006	We obtained from the British bio-venture, Paradigm Therapeutics, and the rights to develop NCEs for the central nervous disorder owned by the said company for the next 3 years.
2006	We obtained from the German bio-venture Evotec Neurosciences, and the rights to develop NCEs for Alzheimer disease, which we conducted collaborative research.
2006	We obtained from the U.S. bio-venture XOMA, and the rights to develop NCEs for drugs used in the treatment of cancers and rheumatism.

Source: This Table was compiled from Nihon Keizai Shimbun.

Notes: NCEs: New Chemical Entities

Table 4: Conditions of the Development of Introduced Research Output

Brand name (Developing code)	Generic name	Introduction			Development in Japan		Development in US		Development in EU	
		From	Year	Area	Phase	Company	Phase	Company	Phase	Company
(TAK-128)	TBD	Mitsubishi Pharma	2001	US+EU+Japan	Phase II	Takeda	Phase II	Takeda	Phase II	Takeda
Tavocept	dimesna	BioNumerik	2003	US and Canada		Takeda	Halt	Takeda		
Amitiza	lubiprostone	Sucampo	2004	US and Canada			Approved	Sucampo, Takeda		
(SYR-322)	TBD	Syrrx (acquisition)	2005	Worldwide	Phase I	Takeda	Phase III	Takeda	Phase III	Takeda
Hematide	TBD	Affymax	2006	Worldwide	Phase I	Takeda	Phase II	Takeda	Phase II	Takeda
(XEN401)	TBD	Xenon	2006	7 countries in Asia						

Source: This Table was compiled from Documents by Takeda Pharmaceutical Company.

Notes: Only those that have been introduced into the Japanese market have been excluded. Such manner of introduction also existed in the 1990's.

TBD: to be determined

Table 5: Research Output by Takeda during the 2000's

Brand name (Developing code)	Generic name	Development in Japan		Development in US		Development in EU	
		Phase	Company	Phase	Company	Phase	Company
(TAK-559)	TBD	Halt	Takeda	Halt	Takeda	Halt	Takeda
(TAK-242)	TBD	Phase III	Takeda	Approved	Takeda	Phase III	Takeda
Rozerem	ramelteon	Phase III	Takeda	Approved	Takeda	Phase III	Takeda
(TAK-475)	TBD	Phase I	Takeda	Phase III	Takeda	Phase III	Takeda
(TAK-390MR)	TBD	Phase I	Takeda	Phase III	TAP	Phase III	Takeda
(TAK-428)	TBD			Phase II	Takeda	Phase II	Takeda
(TAK-654)	sipoglitazar	Halt	Takeda	Halt	Takeda	Halt	Takeda
(TAK-536)	TBD			Phase II	Takeda	Phase II	Takeda
(TAK-583)	TBD	Phase I	Takeda	Phase II	Takeda	Phase II	Takeda
(TAK-491)	TBD			Phase II	Takeda	Phase II	Takeda

Source: This Table was compiled from Documents by Takeda Pharmaceutical Company.

Notes: TBD: to be determined

that this occurred because Takeda did not have many opportunities to contact research output from overseas corporations. After 2003 when the investigation of research output from overseas corporations began, Takeda conducted development, introducing research output from overseas pharmaceutical corporations (Table 4).

As we have seen from the above, after 2001, R&D activities of Takeda changed from research-focused activities to development-focused activities. It may be said that especially from 2003, with the start of the introduction of research output from overseas companies, the change in R&D activities to development-focused activities hit full swing.

However, this case does not intend to show that Takeda's R&D activities were specialized to the development activities. Takeda did not externalized its research activities completely, but was still performing its own research activities. The above-mentioned case indicates that the R&D changed from research-focused activities to development-focused activities, does not indicate that the R&D changed from research activities to development activities.

For reference, the current research output by Takeda is shown in Table 5. It indicates that the research output may be insufficient, but Takeda is engaged in research activities even today.

4. Conclusion

This article could show that the R&D activities of a pharmaceutical company change from research-focused activities to development-focused activities, as the scale of the company expands.

In Section 2, we divided R&D of a pharmaceutical company into the research process and the development process, and described each process in detail. As a result, we could realize that while scale does not affect research output, it does positively affect development output. It is suggested, therefore, that R&D activities of pharmaceutical corporations may change from research-focused activities to development-focused activities, along with scale expansion.

In Section 3, using Takeda as an example, which rapidly enlarged its corporate scale since the 1990's, we could verify that R&D activities change from research-focused activities to development-focused activities.

The cause of such a change lies in the difference in determinant factors of research output and development output as shown in Section 2. Since development capability improves with scale expansion, and research capability does not, R&D will change to development-focused activities where capability has increased.

Finally, we would like to mention some possible future research topics.

First, since the conclusion reached in this article is based only on the example of Takeda, it should be verified as to whether the same conclusion can be obtained from other pharmaceutical companies in the U.S. and E.U. which have already experienced scale expansion. If the same conclusion is obtained from these cases, it will be useful to build a developmental model of pharmaceutical companies.

Second, since pharmaceutical companies of Japan other than Takeda have also enlarged their scale since 2000, it is necessary to verify whether the same conclusion can be gained from other Japanese pharmaceutical companies, although this is related to the first issue.

Third, it would be very useful to analyze the process to uncover research output from outside the company, since research would be externalized if R&D of pharmaceutical companies changes to development-focused activities along with scale expansion. Development activities cannot be performed without obtaining research output. Therefore, for a pharmaceutical company whose R&D is development-focused, in order to obtain a new drug as a development output, the process of discovering the external research output becomes very important.

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