Drug Discovery Process: A Case Study on Takeda

Kenichi KUWASHIMA\textsuperscript{a)}

Abstract: In pharmaceutical research and development of drugs, discovering new drugs from a large number of potential alternatives (chemical compounds), which are theoretically as many as \(10^{60}\), is an important challenge. Here the new-drug discovery process was explored through a case study on Rozerem from Takeda Pharmaceutical Company Limited. Although the recent mainstream approach is to generate and test a large number of alternatives using automation technologies, Rozerem was discovered through exploration of a small number of alternatives with rational chemical compound design, based on researchers’ experience and knowledge.

Keywords: drug discovery, pharmaceutical R&D, case study

Introduction

Pharmaceutical research and development of drugs is well-known...
for its high uncertainty (Kuwashima, 2006; Pisano, 2006a, 2006b). The theoretical total of chemical compounds that may become potential new drugs is estimated to be $10^{60}$ (Okuno, 2014). Discovering new drugs from such an enormous number of potential alternatives is an important issue for researchers in pharmaceutical companies (Becker & Lillemark, 2006; Garnier, 2008; Kuwashima, 2015; Pisano, 1997).¹

In this study, the process leading to the discovery of a new drug is explored, focusing on Rozerem (generic name: ramelteon), a therapeutic agent for insomnia released by Takeda Pharmaceutical Company Limited (hereinafter, Takeda) in 2010 (Japan) as an example. In the Japanese pharmaceutical industry, when Rozerem was introduced into the market, the mean number of chemical compounds explored to discover a single new drug was approximately 25,000 (Japan Pharmaceutical Manufacturers Association, 2010). On the other hand, Rozerem was discovered through the exploration of only approximately 300 alternatives.

## Discovery Process of Rozerem²

### (1) Trigger for research

Research and development of Rozerem was initiated under the direction of Katsura Morita, the president of Takeda. At the end of 1991, Morita learned from the press about a variety of social

---

¹ From this aspect, the pharmaceutical industry has attracted attention and has been extensively studied in research areas of R & D and new product development management (e.g., Kuwashima, 2003, 2013; Thomke, 1998; Thomke & Kuemmerle, 2002). However, research conducted on process products, including pharmaceuticals, is much less compared with that conducted on assembly products, such as automobiles and home appliances (Kuwashima, 2012, 2013).

² This case is based on interviews with project leaders and members working on the discovery of Rozerem at Takeda Pharmaceutical Company Limited.
problems because of memory impairment caused by Halcion (generic name: triazolam), a sleep-inducing agent from Upjohn (US) that was dominant in the market. Therefore, he instructed the drug research division to develop a sleep-inducing agent with fewer side effects.

(2) Determining the drug target

In April 1992, the sleep-inducing drug research team was formed in the drug research division and the project started. Initially, the team had five members, including two chemists and three biologists. In this project, Takeda aimed to develop a safer sleep-inducing agent, instead of a drug that has a potent therapeutic effect but also strong side effects, like Halcion. Therefore, the team decided to choose a target different from the GABA receptor, which is the target of Halcion.

The first drug target chosen was camphor, which is a drug used as an anti-inflammatory analgesic. Camphor was considered suitable as a sleep-inducing agent because its chemical structure is partly similar to that of prostaglandins. The hypnotic effect of prostaglandins had just been discovered in the early 1990s. However, when the pharmacological effect was investigated further, it became clear that developing camphor as a sleep-inducing agent was not desirable. The biggest problem was that prostaglandin receptors were distributed throughout the body. The candidate drug must act selectively in the brain to safely serve as a sleep-inducing agent, but this was difficult to achieve with prostaglandins, which have receptors throughout the body.

The next drug target chosen was melatonin, which is a type of hormone. At that time, several studies showed that melatonin may have a coordination effect on the circadian rhythm. However, most of these studies used animal models, and only a very weak

---

3 The biological rhythm repeats in a cycle of approximately one day (24–25 h).
sleep-inducing effect was observed in humans.

After analyzing information on melatonin collected from all over the world, the Takeda research team hypothesized that if a substance with more potent activity than melatonin is synthesized, it may exert a strong sleep-inducing effect on humans. Based on this hypothesis, a study was initiated on determining a melatonin receptor agonist as a new drug target.

(3) Determining the target compound

In this project, the following two criteria were set as requirements for the target compound.

1) The compound should have a more potent pharmacological effect than melatonin and also have a long duration.

2) The compound should not bind to receptors or enzymes other than those in the brain.

In December 1993, research was initiated with the aim of discovering chemical compounds satisfying these two criteria. When the study started, three melatonin receptors MT1, MT2, and MT3 were known, of which MT1 and MT2 were related to the circadian rhythm and affected sleep. Meanwhile, it was known that MT3 was unlikely to be involved in sleep and was probably distributed not only in the brain but also in other organs, such as the heart, liver, and kidney. Therefore, the research team decided to focus on discovery of chemical compounds that bind selectively to MT1 and MT2 receptors only and does not bind to the MT3 receptor.

(4) Discovery of promising compound

At that time, three chemical compounds, including melatonin, were known as melatonin receptor agonists (Figure 1).

---

4 A chemical compound (key) that binds to the melatonin receptor (lock) and shows a similar pharmacological effect as melatonin.
The team members studied the three chemical compounds in detail and speculated that the structures common to the three chemical compounds [portions in circles and ellipses in Figure 1 (1), (2), and (3)] needed to be maintained, but the central skeleton could be modified. Based on this speculation, the team designed approximately 15 central skeletons and tested if they had the desired pharmacological effect. Therefore, in June 1994, benzocycloalkene derivatives were found to have favorable pharmacological action, and a variety of chemical modifications could be introduced into the structure (i.e., a large number of derivative chemical compounds could be produced) (Figure 2). The team members thought that by taking advantage of this finding, it would be possible to discover a chemical compound that binds to the melatonin receptor even better than melatonin; such a chemical compound could selectively bind only to the melatonin receptor and have a pharmacological activity more potent than melatonin.

Based on benzocycloalkene derivatives that were found to be effective, various derivatives were synthesized, and in March 1995, the team succeeded in discovering an indane derivative (compound A) that showed more potent activity than melatonin (Figure 3, left). In drug development, when an effective chemical compound with an asymmetric center is discovered, the compound is commonly

![Figure 1. Structure of melatonin receptor agonists](image-url)
subjected to optical resolution, and both enantiomers (S- and R-isomers) are evaluated to determine the active ingredient. Thus, compound A was subjected to optical resolution, and it was found that only the S-isomer was capable of strongly binding to the receptor. Based on this result, the synthesis research continued mainly on the S-isomer, and in September 1995, compound B was discovered that binds to the melatonin receptor twice as strongly as melatonin itself (Figure 3, right). The MT3 receptor-selectivity (i.e., how poorly the compound binds to MT3) of compound B was found to be approximately 260 times higher than that for melatonin. The discovery of compound B was thus a major breakthrough in this project.
Drug discovery process

(5) Re-exploration and discovery of “Rozerem”

In early stages of drug development, the initial evaluation (assay) is generally performed in vitro (tests in test tubes), and compounds that give good results are then subjected to in vivo evaluation (tests in living organisms). In this project, after the discovery of compound B, the assay system was changed from in vitro to in vivo in March 1995. However, the compound was not as effective as expected when the evaluation was performed in cats. Compound B was readily metabolized, and the efficacy was thus substantially reduced. Based on this result, the research team resumed exploration in September 1995 to find a chemical compound with high in vivo metabolic stability.

In March 1996, six months after initiating re-exploration, a new chemical compound with high in vivo metabolic stability compound C was discovered. It was later termed as Rozerem (Figure 4). In December 1996, after being observed to be effective in cats and giving good results in monkeys, compound C was assigned a development code of “TAK-375”; it was decided that the compound was to be developed as a candidate for clinical trials. The total number of chemical compounds synthesized until this stage was approximately 300. Thereafter, TAK-375 was tested in clinical trials (1999–2004),

![Figure 4. Structure of compound C (Rozerem)](source: Uchikawa and Okawa (2006).)
approved by the United States FDA (Food and Drug Administration) in July 2005, and released under the trade name of Rozerem in September 2005. It was released in Japan in 2010.

**Discussion**

As can be observed from the above example, there were many trials and errors in the discovery process of Rozerem. For example, the drug target was changed to melatonin because of failure of camphor, and compound B, which was once considered promising, was not successful in animal tests. Rozerem was discovered only through re-exploration. The abundance of trials and errors is common in many other cases of new drug development, including Sankyo’s Mevalotin for treatment of hyperlipidemia, Eisai’s Aricept for treatment of Alzheimer’s disease, and Daiichi Pharmaceutical’s synthetic antimicrobial agent Tarivid (Kuwashima, 1998, 2006). Therefore, Rozerem can be considered as a successful case of drug development.

When research on Rozerem was initiated in the early 1990s, two innovative automation technologies related to drug discovery techniques emerged in the pharmaceutical industry. Combinatorial chemistry and high-throughput screening techniques now facilitate rapid and cost effective synthesis and evaluation of a large number of chemical compounds. Therefore, the mainstream approach in recent drug research and development has been to discover new drugs by screening (exploring) hundreds of thousands of chemical compounds stocked by each company (referred to as a chemical library) (Akaji, Hayashi, & Tsuda, 2014; Sato, 2011). In the case of Rozerem, the success in new drug discovery was through the exploration of a small number of alternatives by rational chemical compound design based on researchers’ experience and knowledge, instead of reliance on the automation technologies mentioned above.
Acknowledgements

This work was supported by JSPS KAKENHI Grant Number 24530451.

References

Akaji, K., Hayashi, K., & Tsuda, Y. (2014). Souyaku kagaku [Medicinal chemistry]. Kyoto, Japan: Dojinsya (in Japanese).
Becker, M. C., & Lillemark, M. (2006). Marketing/R&D integration in the pharmaceutical industry. Research Policy, 35(1), 105–120.
Garnier, J. P. (2008). Rebuilding the R&D engine in big pharma. Harvard Business Review, 86(5), 68–70.
Japan Pharmaceutical Manufacturing Association (2010). Tekisuto bukku iyakuhin sangyo [Textbook pharmaceutical industry]. Tokyo, Japan: Japan Pharmaceutical Manufacturing Association (in Japanese).
Kuwashima, K. (1998). Patterns of new product development in Japan’s pharmaceutical industry: The case of Mevalotin. In E. Geisler & O. Heller (Eds.), Management of medical technology-theory: Practice and cases (pp. 459–468). Boston, MA: Kluwer Academic.
Kuwashima, K. (2003). Organizational capability and competitive advantage in pharmaceutical product development. Annals of Business Administrative Science, 2, 21–27. doi: 10.7880/abas.2.21
Kuwashima, K. (2006). Fukakujitusei no manejimento [Management of uncertainty]. Tokyo, Japan: Nikkei BP (in Japanese).
Kuwashima, K. (2010). Iyakuhin no inobe-syon purosesu to manejimento [Pharmaceutical innovation process and management]. Akamon Management Review, 9(12), 873–918 (in Japanese).
Kuwashima, K. (2012). Product development research cycle: A historical review 1960s–1980s. Annals of Business Administrative Science, 11, 11–23. doi: 10.7880/abas.11.11
Kuwashima, K. (2013). Followers of Harvard Study: A review of product development research 1990s–2000s. Annals of Business Administrative Science, 12, 31–44. doi: 10.7880/abas.12.31
Kuwashima, K. (2015). Exploring the characteristics of pharmaceutical
product development: A cross-industry perspective. *Annals of Business Administrative Science*, 14, 161–170. doi: 10.7880/abas.14.161

Okuno, Y. (2014). Supakon souyaku kara mieru inshiriko no mirai [Supercomputer offers a glimpse of the future of in silico drug discovery.] *Journal of Pharmaceutical Science and Technology*, 74(5), 327–334 (in Japanese).

Pisano, G. P. (1997). *The development factory: Unlocking the potential of process innovation*. Boston, MA: Harvard Business Press.

Pisano, G. P. (2006a). Can science be a business? *Harvard Business Review*, 10, 1–12.

Pisano, G. P. (2006b). *Science business: The promise, the reality, and the future of biotech*. Boston, MA: Harvard Business Press.

Sato, K. (2011). *Souyaku kagaku nyumon* [Introduction to pharmaceutical sciences]. Tokyo, Japan: Ohmsha (in Japanese).

Thomke, S. H. (1998). Managing experimentation in the design of new products. *Management Science*, 44(6), 743–762.

Thomke, S., & Kuemmerle, W. (2002). Asset accumulation, interdependence and technological change: Evidence from pharmaceutical drug discovery. *Strategic Management Journal*, 23(7), 619–635.

Uchikawa, O., & Okawa, S. (2006). Fuminsyou chiryoyaku Rozeremu no oitachi [History of drugs for insomnia “Rozerem”]. *Kinki Chemical Society*, (2006, October), 1–8.