1. Introduction

1.1 UNDERSTANDING THE PROCESS OF DRUG DISCOVERY AND DEVELOPMENT

This study is an attempt to explore the process of technological change, particularly in pharmaceuticals. Pharmaceuticals are important products for our lives. They are indispensable for patients. They are often lifesaving. Some of them are not lifesaving but improve the quality of life. The longer the lives of people become, the more beneficial this type of drug will be. However, at the same time, they are potentially dangerous. Their wrong administration may cause death or serious damage. Mainly because of this, modern governments strictly regulate every aspect of the industry: research, development, manufacturing, marketing and delivery. Enormous sums of public money are spent on the distribution and regulation of pharmaceuticals. In addition, the pharmaceutical industry becomes more and more important for the competitive advantage of industrialized countries. The production of pharmaceuticals requires high-quality skills, sophisticated equipment, and a highly controlled environment. Moreover, research and development (R&D) for new pharmaceuticals is on the cutting edge of biomedical sciences. The pharmaceutical industry is one of the most research-intensive industries. R&D costs in the industry are more than 10 per cent of sales (Association of the British Pharmaceutical Industry 1997, p. 29; Japan Pharmaceutical Manufacturers Association 1997, p. I-35). They are also the main outlet of biomedical and other researches conducted in academic institutions, and contribute to the justification of investment in those researches. The pharmaceutical industry also supports various industrial and professional activities because it takes about a decade involving a complex procedure and costs a huge amount of money to develop a drug. Thus, pharmaceuticals can be regarded as one of the most crucial technologies, in particular for industrialized countries.

Despite the importance of pharmaceuticals, outsiders including social scientists only partly understand the process by which drugs are shaped. As will be seen in Chapter 2, a large body of literature in economics and management and organization studies has explored the aggregated, abstract and/or cross-sectional pictures of drug R&D. Sociological literature in this
field has described in detail parts of the process of drug R&D. However, there are few empirical studies that examine the social process of drug discovery and development fully and closely. This is possibly because most social scientists hesitate to open the black box of pharmaceuticals, which seems to be formidable stuff. Another possible reason is the high confidentiality of pharmaceutical companies, in which the greater part of the innovation process is included.

Without sufficient empirical investigation, the process of drug discovery and development is sometimes regarded as following the linear model. The linear model of technological change suggests that technological change starts from scientific research, goes through technological development and production, and ends with consumption. An alternative version of the linear model implies that technological change starts from social needs, followed by research and development, production and marketing, and ends with the satisfaction of the initial needs. Nowadays, these linear views of technological change are in general regarded as too simple to represent the actual process of technological change. However, the pharmaceutical industry is sometimes seen as an exception. Indeed, the innovation process in the industry 'looks' as if it were linear, because the government regulates the procedure of drug discovery and development one by one based on a linear scheme. But the appearances and the realities of social phenomena are often different. Without sufficiently detailed empirical studies, how can we say that the innovation process of pharmaceuticals is linear?

The main objective of this study is to fill the gap with a close examination of the process of drug discovery and development. My approach to this target is basically a sociological one, namely the social shaping of technology, which emphasizes the intertwining relationship of society and technology, the myriad ways society shapes technology, the attention to both local and wider societal relationships, the intractability of the material world, and the empirical investigation of the contents of technology and the process of technological change. Although the fundamental discipline of this approach is sociology, a number of concepts and ideas of other disciplines including institutional economics and management studies are also incorporated into the analysis (MacKenzie and Wajcman 1999, pp. xiv–xvii, 3–27; Williams and Edge 1996). This study can be regarded as an attempt to explore the social shaping of pharmaceuticals. It aims to reveal how drugs are shaped in society and what kinds of relationships exist among relevant agents and elements. Not only the sociological aspect of the process but also its economic, organizational and pharmacological aspects are examined.

Based on the view of the social shaping of technology, this book demonstrates the heterogeneity, interactivity, uncertainty and contingency of the process of drug discovery and development. The shaping of
pharmaceuticals is an interesting issue from a sociological point of view, because various social groups seem to be involved in the process. As a result, pharmaceuticals have several different meanings: for researchers, they are chemicals; for patients and doctors, they are therapies; for companies, they are products for sale; for regulators, they are objects of regulation; for some industrial workers, they may be the means of intra-organizational politics. If we divide relevant people into smaller social groups, there are probably even more meanings. For example, chemists and biologists probably attribute different meanings to the same chemical. Patients and doctors probably regard the same medicine as having different therapeutic values. The production and marketing divisions of the same pharmaceutical company probably evaluate the same product from different points of view. Thus, different social groups give different meanings to the same drug. A drug is shaped through interactions among these actors. How do they interact with each other?

Various non-human entities also seem to be involved in the process of drug shaping. It is obvious that without things such as drugs, tissues, animals, experimental instruments, production facilities, computers and means of communication, no drug can be shaped. As will be seen in the next chapter, there is a body of literature discussing the relationship between people and artefacts in the sociology of science and technology. Although this philosophical controversy is beyond the scope of this study, it is certainly interesting for us to look at the roles various non-human entities play in the innovation process of pharmaceuticals. What kinds of non-human entities are involved in the process of drug shaping and how do they interact with human actors?

In addition, institutional and structural factors cannot be ignored in the study of the process of drug shaping. There exist the social relationships that are beyond the interactions between the 'relevant' human actors and non-human entities. No one lacks his/her historical, structural and cultural position and no one can be free from the influences of these positions, though he/she is often unaware of being influenced. Non-humans are also given positions and meanings by institutional and structural factors. For instance, who their possessors are is defined not only by the interactions among directly related social groups but also by institutional and structural factors such as laws, patents and the economic structure. Thus, institutional and structural factors, which are also affected by local history and culture, influence the process of drug shaping. What kinds of institutional and structural factors affect the process and how do they do so?

The influence of historical and structural context on the process of drug shaping is also interesting from the viewpoint of industrial policy. This seems to help us to understand why the pharmaceutical industry in some
states is more successful than in others. In particular, it is often argued that the Japanese pharmaceutical industry is not internationally stronger than its British counterpart though in many other industries Japan is globally stronger than the UK. Why is the Japanese pharmaceutical industry internationally uncompetitive?

In sum, this study aims at answering a set of questions: In what way are drugs discovered and developed? What kinds of human actors are related to the process? What kinds of non-human entities are critical in the process? What kinds of institutional and structural factors affect the process? How do human actors, non-human entities, and institutional and structural factors interact with each other? Can the process of drug shaping be described by the linear model of technological change? If not, what kind of model plausibly describes the process of drug discovery and development? Are there any distinct patterns in the process of drug shaping? How different are the processes in different countries? Why is the Japanese pharmaceutical industry weak? What are the theoretical and practical implications of the findings?

In order to answer these research questions, I conduct multiple case studies consisting of 16 cases of drug discovery and development in different therapeutic areas in Japan and the United Kingdom. To analyse the cases I divide the process of drug shaping into four different aspects, namely the shaping of the compound, the shaping of the application, the shaping of organizational authorization, and the shaping of the market. Relevant human actors, non-human entities, and institutional and structural factors are identified and their interactions are examined. The relationships between different aspects of drug shaping are also investigated. Then, the different cases in different settings are compared, and similarities and differences are explored. Based on these analyses, I discuss the distinct pattern of drug discovery and development, the influences of national settings on the process of drug innovation, and theoretical and practical implications.

1.2 DISTINCTIVE FEATURES OF THIS STUDY

This study possesses two uncommon features compared with most other innovation studies. First, I venture into the contents of relevant academic literature in medicine, physiology and pharmacology. This is because academic literature has a lot of historical evidence and information to help us understand the process of drug shaping. To minimize misunderstanding, I conducted interviews with key researchers and corporate staff who were involved in the discovery and development of the drugs. I also consult other sorts of literature such as review articles, textbooks, biography and corporate
history. I emphasize again that I used the contents of academic literature only as evidence for a sociological and historical study of drug innovation, and that I have no intention of discussing the contents themselves.

The second unique feature of this study is that I also explore the organizational processes inside pharmaceutical companies. This was achieved by interviewing relevant people and consulting some internal documents which were obtained by courtesy of these people or their companies. As mentioned above, pharmaceutical companies are especially sensitive about confidentiality. However, probably because of their awareness of the importance of public relations and because most of the cases I examined were no longer at the cutting edge of research, they were generally cooperative. All the researchers I met seemed proud of their achievements in drug discovery and development, and were happy to talk about them to me. There is again a potential risk as regards the accuracy of their stories. To reduce this risk, I also consulted academic papers, patents and other sources of information. This study demonstrates that a company is not a monolithic unit but that there are a lot of conflicts and politics within it.

1.3 THE STRUCTURE OF THIS BOOK

This book consists of nine chapters. Chapter 2 reviews various perspectives on technological change, in particular, the linear model and its criticism consisting of several non-linear perspectives on technological change. The chapter also describes some basic features of R&D activities in the pharmaceutical industry. Then, literature on drug R&D from different disciplinary viewpoints is reviewed. Based on the literature review, I propose a new framework of analysis for this study, which includes the different aspects of drug shaping: the compound, the application, organizational authorization, and the market. At the end of the chapter, the methodological matters of this study are set out.

In each chapter from Chapter 3 to Chapter 6, several cases of drug discovery and development in the same therapeutic area are described. Each chapter includes at least one British and one Japanese case. Chapter 3 deals with cardiovascular drugs, especially the ones that are used for the treatment of hypertension. The innovation processes of two β-blockers, namely propranolol and atenolol, and of one Ca-antagonist, nicardipine, are examined. Chapter 4 addresses the cases of anti-asthma drugs including β-stimulants such as salbutamol, salmeterol and procaterol, and inhaled steroids such as beclomethasone dipropionate and fluticasone propionate. Chapter 5 describes the cases of drugs called histamine H2-antagonists, used
for the treatment of peptic ulcer. They include cimetidine, ranitidine and famotidine. Chapter 6 depicts the R&D process of two LHRH analogues, leuprorelin and goserelin, which are used in the treatment of prostate and breast cancer and several gynaecological diseases. These case studies revealed the complex interaction between various human actors, non-human entities, and institutional and structural factors in the process of drug discovery and development. In addition, a few different patterns of drug shaping are also found, which are confirmed in Chapter 7.

Chapter 7 explores three more cases of drug discovery and development which took place in Japan. These cases include an HMG-CoA reductase inhibitor, mevastatin, which reduces the level of cholesterol in the blood, an $\alpha_{1c}$-receptor antagonist, tamsulosin, which is used for the treatment of urinary disorder accompanying benign prostatic hypertrophy, and an cephalosporin antibiotic, cefotiam. Although they belong to different therapeutic areas, they are intentionally brought together in order to confirm the findings of previous chapters about the different patterns of drug discovery and development, which I name types of drug innovation. The drugs dealt with in this chapter are clearly different in novelty in terms of chemical structure and medical application. Mevastatin is the exemplary compound of other HMG-CoA reductase inhibitors such as lovastatin, simvastatin and pravastatin. It is paradigmatic as a compound and as a therapy. Therefore, I name this type paradigmatic innovation. Tamsulosin is not very novel as a compound; however, its application is innovative. It is used for the treatment of urinary disorder whereas existing $\alpha$-receptor antagonists are used for the treatment of hypertension. I name this type application innovation. Although cefotiam has some unique structure in its molecule, it is not a paradigmatic drug. It has exemplary compounds and its application is the same as the exemplars. I name this type modification-based innovation. These case studies clarify distinct properties of each type of drug innovation by going into the details of the process of drug discovery and development.

Chapter 8 integrates the findings of empirical studies in previous chapters with the theoretical framework. First, general features of the process of shaping drugs are described. Four different aspects of drug shaping are discussed respectively. Different human actors, non-human entities, and institutional and structural factors involved in each aspect are identified. The interactions between them are also described. In addition, it is argued that the different aspects also interact and are interdependent with each other. Based on these, I suggest an interactive model of drug shaping. Second, based on a comparative analysis of different cases, three different types of innovation in the pharmaceutical industry, namely paradigmatic innovation, application innovation and modification-based innovation, are
explained. The chapter explores several distinguishable characteristics of each type, with regard to interactions between human actors, non-human entities, and institutional and structural factors. Third, based on the comparison between British and Japanese cases, the distinctive features of Japanese pharmaceutical innovation are discussed. Several institutional and structural factors affecting the innovation process are considered. Finally, in Chapter 9 this study ends by summarizing findings and discussing theoretical and practical implications.

NOTE

1. A drug discovery is defined here as a discovery of the ‘fact’ that a natural or synthesized chemical has a profile of biological activity which can be applied to the treatment of diseases. However, from the viewpoint of the social shaping of science and technology, I do not intend to suggest that the ‘fact’ is an objective matter, which exists independently of social processes. I use the words ‘drug discovery’ only for convenience because the usage is common among people.