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Latecomers' science-based catch-up in transition: the case of the Korean pharmaceutical industry

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I dedicate this thesis to my family, my wife Hyun-ah and my son Ji-un.

UNIVERSITY OF SUSSEX

SeongWoong Hwang

Latecomers' science-based catch-up in transition: the case of the Korean pharmaceutical industry

SUMMARY

This thesis investigates the 25-year transitional process of the Korean pharmaceutical industry from its initial focus on the imitative production of generic drugs to the development of new drugs. The catch-up dynamics of latecomer countries in science-intensive industries, such as the pharmaceutical industry, is an overlooked research topic in existing literature on innovation studies. This thesis provides an in-depth analysis of Korea's science-intensive catch-up and applies an 'exploration and exploitation' framework to a latecomer setting and in a novel institutional and market context of the transitional phase.

This thesis argues that the rate of change in the transition from imitating drugs to developing new drugs depends on the institutional and organisational mechanisms that enable a new form of technological learning, termed 'exploratory learning'. This form of learning is often unfamiliar to firms in latecomer countries, whereas it is necessary for producing innovative drugs. That is, latecomers' institutional and organisational promotion of exploratory learning is related to a 'pattern change' in the previously established institutional and organisational routines associated with imitative learning.

The findings show that the rate of industrial transition in this sector was constrained by the problematic operation of S&T policies promoting key characteristics of exploratory learning, such as high-risk long-term learning as well as dense interactions between a diverse number of innovation actors. The findings also illuminate some latecomer firms' initial difficulties in managing the new mode of technological learning, and in strategically applying that mode of learning to overcome the barriers to moving through the transitional phase towards producing competitive innovation.

The thesis also suggests that the nature of drugs as integral products, deeply grounded in science, makes it difficult to effectively promote institutional and organisational transformations in favour of exploratory learning.

TABLE OF CONTENTS

Acknowledgements i

Summary ii

List of Tables ix

List of Figures x

Abbreviations xi

Chapter 1: Introduction 1

1.1 Motivation and Aims 1

1.2 The Empirical Context 3

1.3 The Theoretical Context 7

1.4 Research Strategy, Design, Methods 10

1.5 Structure of the Thesis 11

Chapter 2: Theoretical context 13

2.1 Introduction 13

2.2 Key Concepts of Innovation in the Latecomer Context 14

2.2.1 Uncertainty, innovation, learning and resources 14

2.2.2 Latecomers' technological capability 16

2.2.2.1 Concept 17

2.2.2.2 Stages of technological capability building 18

2.2.2.3 Driving force of technological capability 19

2.2.2.4 Technological capability in the transitional phase 20

2.2.3 Micro-dynamics of innovation: organisational learning 20

2.2.3.1 Definition 20

2.2.3.2 Exploitation and exploration 22

2.2.3.3 The vulnerability of exploratory learning 23

2.2.3.4 Exploratory learning in the transitional phase 23

2.2.4 Macro-dynamics of innovation: innovation systems 24

2.2.4.1 National and sectoral innovation systems 25

2.2.4.2 Innovation systems in the transitional phase 27

2.3 Technological Capability in the Transitional Phase 27

2.3.1 Micro-level dynamics 28

2.3.1.1 Features of rapid catch-up 28

2.3.1.2 Technological capability in the transitional phase 29

2.3.1.3 Changing nature of technological learning 34

2.3.2 The macro-level dynamics 35

2.3.2.1 Features of institutional conditions 35
2.3.2.2 Innovation systems in transition 47
2.3.2.3 Changing institutional conditions 40
2.4 Nature of Innovation in the Pharmaceutical Industry 40
2.4.1 Science-based innovation 41
2.4.1.1 Basic institutions 41
2.4.1.2 Science-driven learning and innovation 42
2.4.2 The emerging biotechnology paradigm 43
2.4.3 Product nature as an integral product 45
2.4.4 Impact of the knowledge base on pharmaceutical R&D 45
2.5 New Challenge: Understanding of Science-Based Catch-up 47
2.5.1 Challenges for science-based transition 47
2.5.2 Key characteristics of exploratory learning 49
2.5.3 Limited understanding of science-based catch-up 50
2.6 Summary 51

Chapter 3: Research Questions, Frameworks and Methodology 52
3.1 Introduction 52
3.2 Research Issues and Research Questions 52
3.2.1 Research issues 52
3.2.2 Research objective and questions 54
3.3 Theoretical Framework 56
3.3.1 Sectoral transition as transformational process 56
3.3.2 System-level transformational process 57
3.3.2.1 S&T policies: investment, incentive, industrialisation and alignment 58
3.3.2.2 Behavioural pattern of exploration practices 61
3.3.3 Firm-level transformational process 61
3.3.3.1 Technological development practices 62
3.3.3.2 Organisational mechanisms 63
3.4 Analytical Framework 65
3.4.1 System-level analytical framework and its elements 65
3.4.2 Firm-level analytical framework 67
3.5 Methodology 69
3.5.1 Research strategy and design 69
3.5.1.1 Rationale of the conceptual framework 70
3.5.1.2 Embedded single case study 70

3.5.1.3 Dynamic view of the research issue 71
3.5.2 Methods of data collection 71
3.5.3 Analysing the data 75
3.6 Summary 76

Chapter 4 Research Context 77
4.1 Introduction 77
4.2 Overview of the Pharmaceutical Industry 77
4.2.1 Technological context 77
4.2.1.1 Product development 78
4.2.1.2 Process development 81
4.2.1.3 Latecomers' approach 82
4.2.1.4 Decreasing R&D productivity 83
4.2.2 Market context 85
4.2.2.1 Conventional business model 85
4.2.2.2 Changing business model 88
4.3 Institutional Environment of the KoPI 89
4.3.1 Mastering imitative technologies in the 1970s 89
4.3.2 Major institutional changes 90
4.3.2.1 Reinforcement of product patent in 1987 91
4.3.2.2 Reform of national health insurance in 2000 92
4.4 Changing Market Selection Criteria 93
4.4.1 Prior to the reform of NHI 93
4.4.2 After the reform of the NHI 94
4.4.3 Intermediate outcome of the change 95
4.5 Changing S&T Policy Landscape 97
4.5.1 Disappearance and reappearance of industrial policies 97
4.5.2 National attention to biotechnology 98
4.5.3 Changes in detailed S&T policies for R&D support 102
4.6 Summary 103

Chapter 5: The rearranged S&T Policies and Exploratory Learning 105
5.1 Introduction 105
5.2 R&D Investment for New-drug R&D 105
5.2.1 Positive effects on the promotion of new-drug R&D 106
5.2.2 The mismatch between R&D investment and demand 108
5.3 Incentive Regime of National R&D Programmes 109

5.3.1 Evaluation pattern of national R&D programmes 110
5.3.1.1 Project-based incentive structure 110
5.3.1.2 Dual effects of the project-based system 110
5.3.2 Selection mechanism of national R&D programmes 113
5.3.2.1 Professor-led selection environment 113
5.3.2.2 Problems of the closed policy network 115
5.4 Ministerial Role of Supporting New-drug R&D 117
5.4.1 Governmental structure of drug R&D support 117
5.4.2 Ministry of Science and Technology (MOST) 119
5.4.3 Ministry of Health and Welfare (MOHW) 123
5.4.4 Ministry of Trade, Industry, and Energy (MOTIE) 126
5.4.5 Summary of the ministerial role 129
5.5 Effect of Policy Dynamics on Drug R&D Practices 129
5.5.1 Expressed outcomes of the policy dynamics 130
5.5.2 The policy dynamics in view of exploratory learning 132
5.6 Summary 133

Chapter 6: Firms' Exploratory Learning in New-drug R&D 134
6.1 Introduction 134
6.2 Market Position and Technological Level 135
6.3 The First Round of New-drug R&D 138
6.3.1 Initial challenges to new-drug development 138
6.3.1.1 The case of Dong-a 138
6.3.1.2 Learning by failure 140
6.3.2 The first new drug – R&D process and strategy 141
6.3.2.1 Commercial failure 1 – The first global-level drug 143
6.3.2.2 Commercial failure 2 – The most innovative drug 146
6.3.2.3 Commercial failure 3 – The longest R&D 148
6.3.2.4 Commercial success – Drug for local & niche 150
6.4 The Second Round of New-Drug R&D 153
6.4.1 Process innovation– Incrementally modified drugs 154
6.4.2 Product innovation– Quality-of-life drugs 157
6.4.3 Product innovation– Phytomedicines 160
6.4.4 Product innovation– Biological drugs 162
6.5 Features of Drug R&D in View of Exploratory Learning 165
6.5.1 The first round of new-drug R&D 165
6.5.2 The second round of new-drug R&D 168

6.6 Summary 170

Chapter 7: Organisational Changes in New-drug R&D 171

7.1 Introduction 171

7.2 Organisational Structure for New-drug R&D 171

7.2.1 Change in the R&D organisation of Dong-a 171

7.2.2 Lag in restructuring R&D organisation 176

7.2.3 The arm's length R&D organisation 180

7.3 Summary 182

Chapter 8: Analysis and Discussion 183

8.1 Introduction 183

8.2 Institutional Factors Influencing Exploratory Learning 184

8.2.1 Literature and empirical findings 184

8.2.2 Investment policy 188

8.2.2.1 Direction, manner and outcomes 188

8.2.3 Incentive regime 189

8.2.3.1 Dual effects on exploratory learning 190

8.2.3.2 Institutional inertia in the incentive regime 192

8.2.4 Industrialisation policy 193

8.2.4.1 Policy pattern of the three ministries 194

8.2.4.2 Inter-ministerial compartmentalisation 196

8.2.5 Policy alignment 197

8.2.5.1 Failure to align diverse incentives 197

8.2.5.2 Product nature and inter-ministerial relationship 199

8.2.6 Overall findings of Research Question 1 200

8.3 Organisational Factors Influencing Exploratory Learning 202

8.3.1 Literature and empirical findings 203

8.3.2 Exploration practices in new-drug R&D 205

8.3.3 R&D strategy in the transitional phase 206

8.3.3.1 Time-to-market of exploratory learning 206

8.3.3.2 The paths of exploratory learning 209

8.3.3.3 The scale of exploratory learning 211

8.3.4 Organisational mechanism 211

8.3.4.1 Delay in changing R&D organisational structure 212

8.3.4.2 The arm's-length R&D organisation 213

8.3.4.3 Role of top management and ownership 215

8.3.4.4 The latecomers' organisational code 215
8.3.5 Overall findings of Research Question 2 218
8.4 Summary 220

Chapter 9: Conclusion 222
9.1 Introduction 222
9.2 Empirical Findings 223
9.2.1 Transition in the science-based pharmaceutical industry 224
9.2.2 Institutional mechanisms of exploratory learning 225
9.2.3 Organisational mechanisms of exploratory learning 227
9.3 Theoretical Contribution 229
9.3.1 Science base, product nature and catch-up 229
9.3.2 System perspective of exploratory learning 229
9.3.3 Transformative capacity 230
9.3.4 Non-technological factors 231
9.4 Implications in Practice 231
9.4.1 Implications for S&T policies 231
9.4.2 Implications for innovation management 232
9.5 Limitations and Possible Further studies 233
9.6 Final remarks 234

References 236
Appendices 254

List of Tables

Table 1.1: List of new synthetic drugs developed by Korean firms 4
Table 2.1: Key characteristics of exploration in science-based industries 49
Table 3.1: Conceptual framework of a latecomer sectoral transition 57
Table 3.2: Types of data about macro-level environmental conditions 72
Table 3.3: Types of data about micro-level firms..... 72
Table 3.4: Overview of interviews 73
Table 4.1: Key perspectives of the process development 82
Table 4.2: Sales size of Big Pharma in 1990 and 2009..... 85
Table 4.3: Classification of drugs..... 87
Table 4.4: Top 10 ETC drugs and firms 96
Table 4.5: Key S&T policies for the development of the biotechnology 99
Table 4.6: Main NRDPs related to drug R&D 100
Table 4.7: Public R&D spending on biotechnology 101
Table 5.1: Government drug R&D investment classified by actors in 2007 106
Table 5.2: Distribution of committee members in the NSTC by affiliated fields 114
Table 5.3: Distribution of committee members on the HT Programme in 2006..... 114
Table 5.4: Frontier R&D programmes for biotechnology 120
Table 5.5: Projects in the biotechnology-related Frontier Programme broken down by programme/project leader 121
Table 5.6: Number of new DBFs by year 126
Table 5.7: Main fields of the major R&D programmes by MOTIE 127
Table 5.8: Inter-ministerial comparison of institutional momentum 129
Table 6.1: Case firms' sales ranking between 1985 and 2011 135
Table 6.2: New-drug pipelines of case firms in 2012..... 136
Table 6.3: Dong-a's patenting trends, broken into technological focal areas..... 139
Table 6.4: Trials to develop NCEs in the initial stage of new-drug R&D 141
Table 6.5: The NCE pipelines of non-antibiotic and anti-cancer in 2012 158
Table 6.6: KFDA approval of phytomedicine clinical trials 160
Table 6.7: Comparisons between NCEs and phytomedicines 161
Table 6.8: Dong-a's R&D achievements in biotechnology 163
Table 6.9: Biotechnology R&D pipelines of the case firms 165
Table 6.10: Summary of the development of the first new drugs by case firms 166
Table 6.11: Diversification of R&D pipelines 168
Table 6.12: Patent trends of all case companies, by R&D field 169
Table 6.13: Distribution of R&D personnel in the KoPI, by product field 169
Table 7.1: Summary of the restructuring of internal R&D organisations 180

Table 8.1: Summary of institutional and organisational dynamics 187

List of Figures

Figure 2.1: Flow of the research design 13
Figure 2.2: Technological catch-up trajectory 19
Figure 2.3: Technological evolution of drug R&D 44
Figure 3.1: Formulation of research questions and frameworks 52
Figure 3.2: The transformative view of the sectoral transition 56
Figure 3.3: System-level analytical framework of the transition of the KoPI 66
Figure 3.4: Firm-level analytical framework of the transition of the KoPI 68
Figure 4.1: The process of new-drug R&D 79
Figure 4.2: Technological catch-up pattern reversing the PLC 83
Figure 4.3: Annual number of NDA filed with the US FDA 84
Figure 4.4: The market life cycle of drugs in a class 86
Figure 4.5: Import and export trend in the pharmaceutical industry 90
Figure 4.6: The change in the pharmaceutical market after SPD in 2000 95
Figure 4.7: Government investment in drug R&D 101
Figure 4.8: Number of industrial researchers with PhD, master and bachelor degrees 102
Figure 5.1: The performance of biotechnology R&D in the transitional period 107
Figure 5.2: Patent performance of innovation actors in drug R&D 108
Figure 5.3: Amount of drug R&D funding support by ministry 118
Figure 5.4: Governance structure of GRIs surrounding new-drug R&D 119
Figure 6.1: Catch-up pace between the first NCE and follow-up NCEs 142
Figure 6.2: Ciprofloxacin and its formula modification to Gemifloxacin 143
Figure 6.3: Structural formula of Revaprazan and other PPI drugs 147
Figure 6.4: Modification of the first-in-class NCE of Viagra to Zydena 151
Figure 7.1: The change in R&D organisation of Dong-a 174
Figure 7.2: The organisational structure of the R&D centre of Yuhan (after 2009) 176
Figure 7.3: The operation of the R&D organisation of Yuhan (after 2009) 177
Figure 7.4: The organisational structure of the R&D centre of LGLS 179
Figure 8.1: Redirecting new-drug development 208

ABBREVIATIONS

API	Active pharmaceutical ingredients
APA	Active pump antagonist
ARB	Angiotensin-II type beta blocker
Big Pharma	Big pharmaceutical companies
CEO	Chief executive officer
CKD	Chong Keun Dang Pharmaceutical
CTO	Chief technology officer
DBFs	Dedicated biotechnology firms
DDS	Drug delivery system
ETC drugs	Ethical drugs
EOI	Export-oriented industrialisation
FDA	Food and Drug Administration
FTA	Free trade agreement
GC	Green Cross
GERD	Gastroesophageal reflux disease
GRIs	Government research institutes
H2RA	H2 Receptor Antagonists
ICTs	Information and communication technologies
IMD	Incrementally Modified Drug
IND	Investigational new drug
IPRs	Intellectual property rights
ISI	Import-substituting industrialisation
KDRA	Korea drug research association
KFDA	Korea Food and Drug Administration (MFDS since 2013)
KHIDI	Korea health industry development institute
KoPI	Korean pharmaceutical industry
K-Pharma	Korean pharmaceutical company
KPMA	Korea pharmaceutical manufacturing association
KRW	Korean Won (currency)
LG LS	LG Life Sciences

MBRI	Mogam Biotechnology Research Institute
MOHW	Ministry of health and welfare
MOST	Ministry of science and technology (MSIP since 2013)
MOTIE	Ministry of trade, industry and energy
NCEs	New chemical entities
NDA	New drug application
NHI	National Health Insurance
NIEs	Newly industrialised economies
NIS	National innovation system
NMEs	New molecular entities
NRDPs	National R&D Programmes
NSTC	National Science and Technology Commission
OBM	Own brand manufacture
ODM	Original design manufacturing
OECD	Organization for Economic Cooperation and Development
OEM	Original equipment manufacturing
ONP system	Officially notified price system
OTC drugs	Over-the-counter drugs
PBS	Project-based system
PLC	Product Life Cycle
PPI	Proton pump inhibitor
QOL	Quality of life
R&D	Research and development
SIS	Sectoral innovation system
S&T	Science and technology
SMEs	Small and medium enterprises
SPD	Separation of prescribing and dispensing
TRIPS	Trade-related aspects of intellectual property rights

Chapter 1: Introduction

1.1 Motivation and Aims

This thesis examines the 25-year transition of the Korean pharmaceutical industry (KoPI), from its initial focus on the imitative production of generic drugs to its more recent focus on the development of new drugs. The research was initially motivated by an interest in the process of catch-up in science-based industries.

A preliminary investigation identified some of the institutional and technological initiators of science-based catch-up in the KoPI, its main industrial players and its overall transition rate. First, a series of changes ranging from intellectual property rights (IPRs) to national health insurance (NHI), and a new biotechnological paradigm in the industry, seemed to initiate and accelerate the transition. Second, the demographic characteristics of the KoPI are also interesting, as the main industrial players are typically small- and medium-sized companies, unlike other industries in South Korea, which are led by large conglomerates known as *Chaebol*.

Third, the present market and technological position of the KoPI indicates the overall rate of transition. On the one hand, the 25-year transition has witnessed the accumulation of innovative technological capabilities, at least to some extent. More than 25 new drugs acquired new drug applications (NDAs) from the Korea Food and Drug Administration (KFDA), and two of them acquired an NDA in the US.[1] On the other hand, notwithstanding the significant technological efforts in the industry, the preliminary data suggests the market performance of the new drugs developed in the KoPI has been relatively insignificant.

Four bodies of innovation-related literature (organisational learning, innovation systems, latecomers' technological capability building and science-based innovation) theoretically underpin the research process of this thesis. It draws on studies that deal with changing patterns of technological learning during the transitional phase, on both an organisational and an institutional level. It also uses studies on sector-specific knowledge dynamics in the pharmaceutical industry, such as science-based innovation and the integral product architecture of drugs.

[1] In 2003, Factive, developed by LG Life Sciences, acquired an NDA in the US. In 2014, Sivexstro, developed by Dong-a, acquired an NDA.

Based on the literature, the thesis assumes that, to a large extent, the rate of the transition may depend on the effective enhancement of a new mode of technological learning: exploratory learning. Subsequently, it also assumes that the enhancement of exploratory learning is affected by a series of institutional and organisational mechanisms, such as science and technology (S&T) policies and firms' organisational structures.

However, there is a lack of studies on latecomers' enhancement of the exploratory mode of technological learning for science-based transition. Most literature on industrial catch-up has focused on modular product-based industries driven by engineering and technology-based innovation with a relatively short learning cycle. Meanwhile, studies on the pharmaceutical industry have mainly dealt with long-term exploratory learning and science-based innovation in the leading industrial nations, such as the US and UK.

In this regard, the literature gap provides an opportunity to extend knowledge about the transitional phase of latecomers, particularly in the science-intensive and integral product-based pharmaceutical industry. To do so, both the institutional and organisational dynamics involved in the key mode of learning for transition, exploratory learning, are considered. In line with this, two main research issues are explored:

1) How have S&T policy rearrangements affected innovation actors' enhancement of the exploratory mode of technological learning?
2) How have latecomer firms strengthened the exploratory mode of technological learning for new-drug R&D?

Specifically, the thesis examines four perspectives on exploratory learning:

- The influence of the revised S&T policies on exploratory learning in organisations
- The influence of the revised S&T policies on exploratory learning between organisations
- Ways of engaging in exploratory technological learning in new-drug R&D
- Ways of reconfiguring organisational processes to deal with increasing exploratory technological learning

By answering the research questions, the thesis will argue that the enhancement of the new mode of technological learning in the KoPI is highly influenced by both previously established imitation-oriented institutional and organisational mechanisms and new, innovation-oriented institutional and organisational mechanisms. The transitional

process has had both positive and negative effects on the KoPI. It also argues that determining which factors influence exploratory learning may provide a better understanding of the transitional dynamics from imitation to innovation in a science-based industry that produces integral products.

The following four sections will present the empirical (Section 1.2) and theoretical background (Section 1.3) for this thesis, the overall research strategy (Section 1.4) and the structure of the thesis (Section 1.5).

1.2 The empirical context

This section provides an overview of the KoPI in terms of the general market composition of the pharmaceutical industry, and the institutional and technological changes that have occurred within it. It then identifies the present level of technological achievement and market position of the KoPI, which provides a starting point for the research.

First, in general, the global pharmaceutical industry consists of two noticeably different market categories.[2] One is the market for new (original) drugs, often referred to as new chemical entities (NCEs) or new molecular entities (NMEs). The other market is for generic drugs, often called copy drugs. This demarcation directly reflects the large technological and patent gap between innovation-based original drugs and imitation-based generic drugs.

Innovation leadership in the new drug market has long been dominated by a small number of developed countries and their major pharmaceutical companies (so-called 'Big Pharma'), such as the US (Pfizer), the UK (GSK), Germany (Merck), Switzerland (Novartis) and France (Sanofi). These five countries and Japan accounted for more than 80% of the NDA approvals by the US Food and Drug Administration (FDA) between 1998 and 2007 (Kneller 2010).[3]

In the generic drug market, which is based on price competition and process imitation/innovation, the four largest generic companies (Teva, Israel; Mylan and Watson, USA; Sandoz, Switzerland) took almost 40% of the sales in the worldwide generic drug market (Harding 2010). In the past decade, Indian pharmaceutical firms, such as Lupin

[2] The size of the worldwide pharmaceutical market reached US$791 billion in 2010, and about 82% of the total sales occurred in the Triad (the US, the European Union and Japan) (Pharm Exec 2011).
[3] This was 210 of the total 252 new drugs approved in the period, and, in particular, half of all the new drugs by US developers (Kneller 2010). Other developed Western countries, including Australia and Canada, accounted for most of the rest, taking up almost 20% (*Ibid*).

and DRL (Dr Reddy's Laboratory), have rapidly penetrated the growing generic drug market.

The KoPI has enhanced the new-drug development over the last 25 years. This move towards the innovation stage can be seen by looking at the increase in local firms' development of NCEs (Table 1.1). The KoPI saw the first market launch of an NCE in 1999, an anti-cancer drug named Sunfla that was developed by SK Chemical. Based on an average 10-year lead time for drug development, this indicates that the KoPI began, at least partly, an industrial transition from the late 1980s.

Table 1.1: List of new synthetic drugs developed by Korean firms

No	Company	Brand	Indication	NDA	Lead time	Sales size (million $, until 2012)
1	*SK* Chemical	Sunpla	Anti-cancer	1999	10	0
2	Dongwha	Milican	Anti-cancer	2001	8	0
3	JW	Q-Roxin	Antibiotic	2001	11	5
4	*LG* Life Science	Factive	Antibiotic	2002	11	3
5	CKD	Camtobell	Anti-cancer	2003	11	3
6	Yuhan	Revanex	Peptic ulcer	2005	15	4
7	Dong-a	Zydena	ED*	2005	9	18
8	Bukwang	Levovir	Hepatitis B Virus	2006	11	6
9	Daewon	Pelubi	Osteoarthritis	2007	7	5
10	*SK* Chemcial	Mvix	ED	2007	10	1
11	Ilyang	Noltec	Gastric ulcer	2008	22	3
12	Boryung	Canab	Hypertension	2010	12	25
13	JW	Zepid	ED	2011	10	5
14	Ilyang	Supect	Anti-cancer	2012	10	2
15	LG Life Science	Zemiglo	Diabetes	2012	9	3
16	CKD	Duvie	Diabetes	2013	13	-
17	Crystal Genomics	Acelex	Osteoarthritis	2015	14	-
18	Dongwha	Zabolante	Antibiotic	2015	18	-
19	Dong-a	Sivexstro	Antibiotic	2015	10	-
20	Dong-a	Suganon	Diabetes	2015	11	-

Source: Various data sources and each company's web page
* ED: Erectile dysfunction

The industrial transition has been affected by a series of institutional and technological changes. The three most significant of these changes are the enforcement of the product patent system in 1987, the radical reformation of national health insurance (NHI) in 2000 and the proliferation of biotechnology and increasing government attention paid to this new technological paradigm since the 1990s.

First, along with some other newly industrialised economies (NIEs), such as Taiwan in 1986 and Canada in 1987, Korea introduced the product patent system in 1987, becoming the first late-industrialising country to adopt the rule (Qian 2007). This was the beginning of the link between international trade and IPR, which was spearheaded by the US as an early version of trade-related aspects of intellectual property rights (TRIPS) (Nam 2006b). The product patent system first pushed new-drug R&D in the KoPI beyond the imitative learning of process technologies for producing generic drugs.

Second, Korea entirely reformed its NHI system in 2000. The introduction of a system for the separation of prescribing and dispensing (SPD) was the most significant change.[4] The reformed NHI had a direct effect on the KoPI, leading to a radical change in market structure. The ethical (ETC) drug market became the major market segment, overtaking over-the-counter (OTC) drugs. This market change forced local pharmaceutical companies to develop more technologically complex ETC drugs.

Lastly, the KoPI's transition was shaped by the emerging biotechnological paradigm. Some leading local pharmaceutical firms and a few *Chaebol* had been exploring biotechnology since the late 1980s. More importantly, the government began to support this new technological paradigm, predicting that it would become an engine of economic development. In 2010, biotechnology, including healthcare technology, became the second-largest recipient sector of government R&D funding, narrowly following information and communication technologies (ICTs). In addition to the Ministry of Science and Technology (MOST), several ministries started to support biotechnology. Public innovation actors such as government research institutes (GRIs) and universities have been the main beneficiaries of this national support.[5] At the same time, the government established a new R&D funding system, the so-called project-based system (PBS), for facilitating and incentivising innovative research in national R&D programmes (NRDPs).

The KoPI's effort to transition into developing its own new drugs was initiated and accelerated by these three institutional and technological changes.

The KoPI is very dense, full of family-based small and medium enterprises (SMEs), with the exception of a few affiliates of *Chaebol*. This is very different from most other Korean industries, which are dominated by *Chaebol*. In 2006, 237 drug manufacturers and 351

[4] The reform indicated that the KoPI had been fully incorporated into the public health sphere through the pharmaceutical pricing and reimbursement system.
[5] However, this national effort also had a dark side: for example, the damaging scientific scandal surrounding supposed stem cell cloning, led by Dr Woo-seok Hwang in 2006, revealed the hastiness of Korea's strong desire to lead in biotechnology (e.g., Gottweis and Triendl 2006, Gottweis and Kim 2010).

pharmaceutical ingredients manufacturers were in operation in Korea (Yeo 2008). Still, no domestic firms have grown to the degree where they can conduct the full development cycle of a new drug from discovery to NDA at the global level.[6]

In terms of performance, the present speed of the industrial transition can be explained by the outcomes of technological and market catch-up in the new drug business. At the beginning, the KoPI showed a certain degree of technological catch-up. About 16 NCEs have been licenced to Big Pharma and Japanese companies since 1989, and 19 NCEs have been approved by the KFDA (Table 1.1). LG Life Sciences (LGLS) became the first domestic firm to acquire NDA approval from the US FDA for Factive (an antibiotic) in 2003, followed by Sivexstro (an antibiotic) in 2014, which was developed by Dong-a. In this regard, it is clear that KoPI has, to some extent, reduced the technological gap between itself and the leading pharmaceutical industries. The KoPI's technological performance in new-drug R&D also indicates a continuous enhancement of the exploratory mode of technological learning.

However, in terms of market catch-up, the KoPI failed to realise the expected market profits from the new drugs. The industry's first new drug, Sunfla, was withdrawn from the market because of a sales slump, and Factive has been seen as a failure in global marketing. Overall, few new drugs, either in the domestic or the global market, have allowed domestic firms to take a meaningful position as innovators, thus cementing their role as copycat drug producers. Additionally, even in the global generic drug market, the KoPI has not been able to obtain significant market share despite its mastery of synthesising existing active pharmaceutical ingredients (APIs).

Therefore, the intermediate outcome, after about 25 years of new-drug R&D, can be described as a bumpy transition with certain interrupting factors. At first glance, these factors seem to be directly associated with firms' R&D and marketing activities. Also, there is the institutional influence on new-drug R&D and business in that the series of institutions surrounding the KoPI have changed.

If the process of industrial transition had not been disturbed by certain factors, the KoPI would presumably have shown a more consistent performance between technological and market catch-up and, ultimately, a faster rate of transition than has occurred. This

[6] In general, new drug development is estimated to cost about US$1 billion for each NCE. Hereafter, the NDA at the global level indicates the NDA approved by the US FDA due to market and regulatory leadership by the US in the industry.

recognition of the present position of the KoPI becomes the starting point of the attempt in this thesis to understand the transitional process of the KoPI in depth.

1.3 The Theoretical Context

This thesis is theoretically underpinned by four bodies of literature. First, two theoretical areas of innovation provide the key underlying concepts of the study: a) organisational learning and b) innovation systems. Two areas of contextual literature related to the KoPI are also drawn upon to interpret the industrial transition of the KoPI: c) latecomers' technological catch-up and d) science-based innovation.

a) Recent research on innovation refers to organisational learning as a learning process through which new products and processes are generated (e.g., Stata 1989, Lundvall and Johnson 1994, Buckler 1996, Beckman and Barry 2007). This approach to innovation as a learning process is grounded in the question of how to bring about innovation rather than simply how to observe innovation (e.g., Senker 1996, Van de Ven et al. 2008). In reality, as will be seen in an examination of the KoPI's transitional process, focusing on processes of change seems to be more effective for understanding how countries, industries and firms organise means of innovation and engage in real practises that spur innovation.

More specifically, the way in which firms innovate can be seen through two perspectives on the learning process: technological and organisational. Bell and Pavitt (1995) emphasise that technological capability encompasses both the accumulation of technological knowledge and the development of corresponding organisational factors. In particular, the transitional phase increases the need for non-technological strategic and organisational perspectives in building technological capability (e.g., Dutrénit 2000, Hobday et al. 2004).

In line with this, this thesis draws on the concept of organisational learning as a comprehensive term that embraces both technological and organisational perspectives on learning. In particular, literature on the two different types of organisational learning, exploitation and exploration, is addressed (e.g., March 1991, Levinthal and March 1993). Exploitation refers to the use of 'things already known', whereas exploration is 'a pursuit of new knowledge' (Levinthal and March 1993). Because of the different natures and goals of these two types of learning, they lead to trade-offs in a firm with limited resources (e.g., Leviathan and March 1993, Benner and Tushman 2003).

Latecomer countries or firms in the transitional phase are faced with the task of developing more innovative products and processes, beyond just imitating dominant designs. This implies a need for enhancing exploratory modes of learning. In this context, this thesis draws upon literature on organisational learning combined with traditional technology-centred studies on innovation (e.g., Bell and Pavitt 1997, Kim 1997a, 1997b).

b) The innovation system is a common conceptual approach used to identify institutional conditions and how they promote or inhibit innovation actors' technological learning (e.g., Freeman 1987, Lundvall 1992, Nelson 1993). This systemic approach considers the individual actors' collective and interactive relationships in generating and diffusing innovation under certain institutional circumstances. The thesis examines two types of innovation systems, the national innovation system (NIS) and the sectoral innovation system (SIS). The NIS refers to the structural differences in production systems and institutional setups, such as S&T policies and financial and educational systems, and their influence on the nation's innovation patterns and performance (e.g., Lundvall 1992, Anderson and Lundvall 1997). The SIS refers to the innovation pattern of an industry. It focuses on the relationship between sector-specific knowledge dynamics, sectoral institutional settings and innovation actors' interactive learning (e.g., Malerba 2002, McKelvey et al. 2004).

Examining the NIS and the SIS is useful because the KoPI's transition has taken place under the influence of broadly national S&T policies as well as the sectoral characteristics of the (Korean) pharmaceutical industry.

c) Although the concept of innovation is commonly used to mean something 'new to the market' (noted by Kaufmann and Tödtling 2001, p. 791), latecomers' innovation activities have been conducted in a manner that is 'new to themselves only'. In other words, latecomers' innovation is characterised by the effective use of imported technological knowledge (Westphal et al. 1985). Many early studies of technological learning adopt this view of innovation to interpret the industrial catch-up at both the institutional and firm levels (e.g., Katz 1987, Amsden 1991, Lall 1992, Hobday 1995, Bell and Pavitt 1997, Kim 1997a, Ernst 1998).

More specifically, in the institutional-level approach, the literature identifies effective policy operation for the establishment of competent private and public innovation actors as the best institutional means to promote knowledge utilisation and commercial performance (e.g., Kim 1997a, Mazzoleni and Nelson 2007). In the firm-level approach, literature often integrates the product life cycle (PLC) model posed by Utterback and

Abernathy (1975) with the absorptive capacity model put forward by Cohen and Levinthal (1990) as a way of understanding latecomer firms' catch-up (e.g., Kim 1997a, Hobday 1995). Stepwise catch-up by rapidly reversing the PLC from the assembly of imported components to the development of their own designed product is a representative example of this approach (e.g., Hobday 1995).

Some recent literature addresses a more advanced catch-up stage, that is, the transitional phase, as some latecomer countries and firms have begun to be more innovative. In the institutional-level approach, the literature examines the transitional process from knowledge utilisation-oriented innovation systems to knowledge generation-oriented innovation systems (e.g., Kim 2000, Dodgson 2009, Vertesy 2013). It focuses on the evolution of the NIS/SIS to deal with the changing knowledge base and competitive environment. The drivers for and barriers to transition are identified in the literature, including institutional flexibility/rigidity and cohesive/incohesive networked learning.

The literature on firm-level transitions examines the increasing complexity of technological and market catch-up in the transitional phase and ways of dealing with this complexity. One group of studies focuses on the process of building innovative capability to develop more novel products and conceptualises certain types of capabilities for transition, such as combinative capability and embryonic strategic capability (e.g., Mathews and Cho 1999, Dutrénit 2000 and 2004). The other studies identify various paths for advanced catch-up. For example, three conceptually possible paths for transition are suggested by drawing on the reversed PLC (e.g., Song et al. 2006 and Choung et al. 2014). Some other studies address the potential of devising firms' own path for transition with respect to the degree of competition with forerunners and the possibility of utilising new technological paradigms (e.g., Hobday 2005, Lee et al. 2005). The path approach can be related to the effectiveness of latecomers' exploratory learning in real competitive environments and amidst a changing knowledge base.

d) Although studies on catch-up provide the broad contextual basis for this thesis, they are not sufficient to interpret the transition of the science-based pharmaceutical industry due to their focus on technology- and engineering-based industries. Literature about science-based innovation in bio-pharmaceutical sectors is drawn on to identify sector-specific knowledge dynamics and learning. First, literature about the nature of science-based innovation is discussed and compared to literature on engineering-based industries (e.g., Pavitt 1998, Pisano 2006). Second, studies on the influence of the emerging biotechnological paradigm in the synthetic chemistry-based pharmaceutical

industry are identified (e.g., Powell et al. 1996, Burns 2005, Pisano 2006). Lastly, literature on the nature of drugs with integral product architecture in comparison with modular products is discussed (e.g., Baldwin and Clark 1997, Pisano 2006).

Overall, by drawing on these four bodies of literature (organisational learning, innovation systems, latecomers' catch-up in transition and science-based innovation), the key characteristics of the exploratory mode of technological learning can be determined; these characteristics are necessary for transition in the pharmaceutical industry. The literature also provides a theoretical basis for the research questions and the conceptual framework of this study.

1.4 Research Strategy, Design, Methods

The transition of the KoPI is investigated using two underlying strategies. First, the changing pattern of technological learning is interpreted in view of the argument that enhancing exploratory learning is the key mode for transition. Second, multi-dimensional perspectives involved in exploratory learning are considered as the foreground of the analysis, including the macro- (institutional) and micro- (firm) levels.

The conceptual framework is built in line with a more transformative view of institutional settings and firms' organisational mechanisms involved in the move from imitation to innovation. More specifically, the framework emphasises the transitional process as the transformation of institutional and organisational mechanisms to promote an exploratory mode of technological learning. In relation to institutional mechanisms, the transformation is seen as the reconfiguration of the innovation system from knowledge utilisation to knowledge generation. S&T policies that influence the reconfiguration of innovation systems are examined, including R&D investment policy, incentive regimes and administrative patterns of governmental R&D support. In the firms' organisational mechanisms, the effective enhancement of the exploratory mode of learning is addressed in terms of R&D process and strategy, and organisational structure.

Because this thesis focuses on the process ('how') of the transition, a case study approach is employed (e.g., Ragin and Becker 1992, Yin 2003). Specifically, an embedded single-case approach is adopted to embrace both macro (innovation systems) and micro (firms) units of analysis, examining national R&D programmes (NRDPs) involving new-drug R&D to investigate the influence of S&T policies in innovation actors' learning patterns, as well as looking at the new-drug development projects of nine domestic pharmaceutical firms.

The data used were mainly collected through formal and informal interviews, in addition to secondary sources such as firm and government reports, business newspapers and patent and publication data. The data were gathered in four broad categories: one related to the environmental changes in institutions, technologies and the market; one related to the operational process of NRDPs; one related to the process of the firms' new drug development (that is, technological learning); and one related to the organisational processes of new-drug R&D.

1.5 Structure of the Thesis

This thesis consists of three main parts. The first part presents the theoretical and methodological foundation of the research (Chapters 2 and 3). The second part empirically analyses the changing market selection environment, and the macro- and micro-level transitional process (Chapters 4, 5, 6 and 7). The last part encompasses the overall discussion and provides a conclusion (Chapters 8 and 9).

In the first part, Chapter 2 reviews the key theoretical concepts of innovation, such as technological capability, organisational learning and innovation systems. Next, the innovation characteristics of the transitional phase and the science-based pharmaceutical industry are illuminated. On this basis, the chapter lays out the key characteristics of exploratory learning in the pharmaceutical industry, which is the key learning pattern for new-drug R&D. This underpins the theoretical constructs and the analytical scheme of this thesis.

Chapter 3 develops the research questions and frameworks and presents research methods and the structure of the data. In particular, an alternative approach to addressing the transition is proposed: the transformative view. This approach considers the need for changes in institutional and organisational mechanisms to promote the exploratory mode of technological learning.

In the second part, Chapter 4 presents the major institutional and technological changes as well as the changed market selection criteria during the transitional period of the KoPI (1987 onwards). The drug R&D process, the changing technological paradigm and the institutional context, such as the IPR regime and the inception of the NHI, are detailed in the latecomer context. Then the industrial response to these – the changing market competition structure – is outlined. Moreover, the overall reform of S&T policies to promote innovation activities is presented, showing that policy changes have directly affected the learning patterns of innovation actors.

Chapter 5 analyses the influence of this S&T policy rearrangement on innovation actors' enhancement of exploratory learning, specifically the operating mechanisms of NRDPs, such as investment, incentives and administrative patterns, and the problems with these mechanisms. This chapter concludes by revealing certain types of institutional distortion and conflict in conducting exploratory learning for new-drug R&D.

Chapters 6 and 7 analyse the new-drug development of the nine case study firms, both in technological learning (Chapter 6) and corresponding organisational perspectives (Chapter 7). Exploration practise and strategic and organisational perspectives are examined in the comparative view between the completed first round and the on-going second round of new- drug R&D. These chapters conclude by identifying the contrasting pattern of technological exploration between the first and second rounds.

In the last part of the thesis, Chapter 8 presents the findings and discusses the overall transitional dynamics of the KoPI. It first determines the ways in which institutional elements have affected the enhancement of exploratory learning: the dual influences of S&T policies on promoting exploratory learning, and the resulting lag of cohesive interaction between public actors' and pharmaceutical firms' exploratory learning. It goes on to discuss organisational elements in relation to the firms' exploratory learning: latecomer firms' blind replication of existing innovation models and their recent search for their own paths of innovation and ideal organisational structure to heighten the commercial viability of exploratory learning. Chapter 9 summarises the research, including the main findings and limitations, and provides some policy and management implications.

Chapter 2: Theoretical context

2.1 Introduction

As methodological literature (e.g., Miles and Huberman 1994, Van de Ven 2007) and recent PhD theses (e.g., Kale 2005, Medeiros 2011) have suggested, the research questions and conceptual frameworks for a thesis are derived from repeated comparison and integration of preliminary data on the thesis topic with the existing literature (Figure 2.1). This research follows this process throughout the literature review chapter (Chapter 2) and research questions and design chapter (Chapter 3) to formulate its research questions and frameworks.

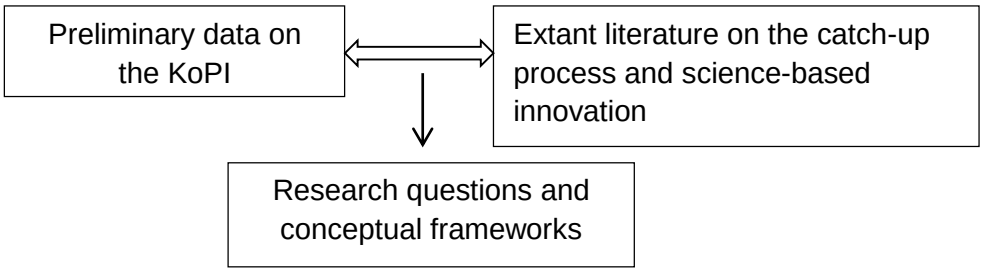

Figure 2.1 Flow of the research design

In line with this, this chapter first considers the extent to which innovation patterns and conditions identified in the existing literature can be applied to the empirical focus of this study, that is, science-based catch-up in the KoPI. More specifically, this chapter first revisits key concepts related to innovation such as technological and organisational learning and innovation systems; it then reviews the literature on catch-up in newly industrialised economies (NIEs) in Asia, and on science-based innovation.

In doing so, the chapter identifies the multi-dimensional complexity of latecomers' science-based innovation in the pharmaceutical industry, and argues that there is a need for institutional and organisational change to promote the key form of technological learning for science-based catch-up, that is, exploratory learning. Based on the literature, it further determines the key characteristics of the exploratory mode of technological learning. The review chapter ultimately provides the theoretical underpinnings for the research questions and conceptual frameworks.

In brief, Section 2.2 presents an overview of the core concepts of innovation in the latecomer context. Sections 2.3 and 2.4 review features of innovation as presented in two bodies of contextual literature. Section 2.5 raises the problem of the limited

understanding of latecomers' science-based innovation activities in the literature and determines the key characteristics of exploratory learning. Section 2.6 summarises the review.

2.2 Key Concepts of Innovation in the Latecomer Context

This section clarifies key theoretical concepts concerning innovation in the transitional phase of the KoPI. First, the fundamental nature of innovation is briefly presented (Sub-section 2.2.1), followed by an overview of innovation in the latecomer context (Sub-section 2.2.2). Then, the concepts and modes of organisational learning and innovation systems are clarified (Sub-sections 2.2.3 and 2.2.4).

2.2.1 Uncertainty, innovation, learning and resources

Recapitulation of key theoretical antecedents of innovation studies provides an effective way of clarifying the general mechanism of innovation. Four key concepts are discussed here: uncertainty, innovation, learning and resources (Knight 1921, Schumpeter 1934 and 1939, Coase 1937, Penrose 1959, Cyert and March 1963).

Uncertainty imposes on firms the need for a continuous organisational response to environmental change over time.[7] It implies dynamic (interactive) organisational responses to the external environment, which includes institutions and other firms. Innovative activity is a major organisational response in that innovation involves the development of new processes and products that allow a firm to survive and grow under conditions of environmental change.[8]

Two original views of firms – the resource-based view (RBV) and the organisational behaviour perspective – argue for two different internal mechanisms for generating innovation: an endogenous base of innovation, and innovation activity as a dynamic organisational process.

First, in the Penrosian view (1959), the extent of a firm's growth is determined by its ability to utilise heterogeneous resources through their variant combinations, thereby creating productive services (Pitelis 2007). The creation of new productive services leads not only to growth in terms of quantitative production, but also to qualitative transformation (Turvani 2007). The latter is realised through reinforcing knowledge about

[7] Knight (1921) classifies the uncertainty into two types: measurable uncertainty and true uncertainty.
[8] Heterogeneity of the firm is raised based on the entrepreneurs' and further organisational differences to operate resources available in responses to uncertainty, as Knight insinuates. Resource-based inter-firm heterogeneity has been increasingly studied in recent innovation studies.

resources and the surrounding environment, which leads to the construction of a firm's distinctive capabilities (*ibid.*).

This interpretation sees innovation as a learning process based on resource management, regardless of whether firms are frontrunners or latecomers. The initial acquisition of resources, their novel combination and the creation of new productive services over time are all caused by the continuous interaction of firms with uncertain environments through internal learning processes based on their resources.

On the other hand, Cyert and March (1963), who conceptualise the firm as an autonomous entity (a discretionary organisation), see internal decision-making processes as organisational responses. The sequence of decisions is coordinated and each is aligned with the others through the four organisational behaviours: quasi resolution of conflict, uncertainty avoidance, problemistic search and organisational learning (*ibid.*).[9]

- *Quasi resolution of conflict* means that firms tend to resolve their intra-organisational conflicts (e.g., different goals and decisions across subunits) through the allocation of specific decision rights to each subunit.[10]
- *Uncertainty avoidance* indicates that the firm strives to avoid rather than predict risk and uncertainty by introducing decision rules, particularly for attending to the near future and arranging the external environment in order to control it.
- *Problemistic search* indicates a passive tendency wherein firms do not start to search for alternatives until they realise or expect some problems, such as falling profits.
- *Organisational learning* is defined as the three different adaptive processes of changing organisational goals, attending new rules and modifying search procedures in coping with an uncertain environment.

These four types of organisational behaviour are combined during searching activities to discover alternatives to problems identified (i.e., the firm’s realignment process between organisational goals, expectations and choice in the changing environment). The searching activity, driven by organisational slack, consists of short-term, problem-oriented search under the pressure of failure to meet organisational goals, and long-term,

[9] The firm as a discretionary organisation is based on the three major assumptions of bounded rationality, imperfect environmental matching and unresolved conflict. The sequence of the decision-making process consists of three major subcategories: organisational goals, organisational expectations and organisational choice.

[10] Quasi resolution of conflict means that firms tend to resolve their intra-organisational conflicts (e.g., different goals and decisions across subunits) through allocation of specific decision rights to each subunit.

innovative activity when firms have enough organisational slack.[11] Cyert and March's argument provides insight into the organisational process of determining the scope and degree of innovation activities in a changing environment, although it is based on the observation of daily work-based decision-making processes.

Overall, these original studies provide complementary theoretical frames for understanding the underlying nature of innovation. Combining these, a firm's innovation activity is treated as a dynamic process of searching for and learning of existing or new opportunities based on their resource holdings. 'Dynamic' mainly indicates that the process is interactive and timely in responding to external environments and organising internal innovation processes. Cyert and March (1963) categorise innovation activity into two types of search and learning patterns: (i) problem solving activity (i.e., proximate searching and learning) and (ii) more innovative activity (i.e., distant searching and learning).

Change in uncertainty and learning type of the KoPI

In the case of the KoPI, which has been in transition over the course of developing several new drugs, the degree of uncertainty and learning type are now changing. Greater involvement in new-drug R&D requires increasingly more distant searching and learning that deviates from the routinised proximate searching and learning carried out when producing copy drugs. This transition implies changing goals, directions and rules for searching and learning. As a result, resource management is likely to need a more dynamic operation in dealing with the transitional phase. The following sub-section clarifies the relevant key concepts of latecomers' innovation activity.

2.2.2 Latecomers' technological capability

Innovation activity in the latecomer context has been commonly understood by drawing on the concept of technological capability, which is defined as 'the ability to make effective use of technological knowledge' (Westphal et al. 1985, p.171). That is, this concept emphasises the utilisation of existing technology for latecomers' innovation. Latecomers are able to acquire existing technologies from advanced countries with no need to develop them on their own. Thus, mastering the imported technologies becomes the most critical learning task. In this context, technological capability building has been viewed as the learning process that allows the proficient use of imported technological

[11] In this sense, the organisational slack can be seen as corresponding to the 'excess resources' proposed by Penrose (Pitelis 2007).

knowledge (Kim 1980, Dahlman and Westphal 1982, Bell 1984, Westphal et al. 1985, Katz 1987, Lall 1992).

This technological capability-centred view of innovation is based on the macro-level evolutionary interpretation of production function through technical changes (e.g, Dosi 1982, Perez 1985, Nelson 1994). At the same time, this view has a micro-level conceptual base of capability and learning (e.g, Selznick 1957, Arrow 1962, Polanyi 1962, Cangelosi and Dill 1965, Nelson and Winter 1982, Cohen and Levinthal 1990, Malerba 1992, Leonard-Barton 1995, Teece et al. 1997). This sub-section describes latecomers' innovation activity within these perspectives on technological capability.

2.2.2.1 Concept

In the literature, latecomers' technological capability is conceptualised based on the level of capability accumulated. For example, Westphal et al. (1985) divide it into three levels: production capability for operating imported production facilities at the beginning level, investment capability necessary for expanding production capacity and new production facilities, and innovative capability that embraces basic and applied research, as well as development activities for developing modified and new processes and products. In the investment capability stage, it is also important to develop non-technological capabilities, because managerial and organisational issues become more complex.

Bell and Pavitt (1997) identify technological capability as the driving force for moving from simple production capacity to further innovative learning stages. Production capacity refers to the resource for the duplicative production of a given production function. In contrast, technological capability refers to growth in the stocks of resources that enable latecomers to generate technical change for improving production efficiency or product quality.[12]

As many scholars have explored empirically (e.g., Dutrénit 2000, Athreye et al. 2009), mastering each level of technological capability and upgrading to the next is achieved through deliberate effort, not automatic processes, such as the accumulation of various types of resources in both technological and non-technological contexts.

[12] Resources are exemplified as skills, knowledge, and institutional structures and linkages, while resources of production capacity are mainly related to the operation of a given level of production function, such as equipment and labour skills that are often guided by technology transfer (Bell and Pavitt 1997). In particular, knowledge has increasingly gained attention as a major constituent of the stocks of resources, in investigating the internal learning process of building/enhancing technological capability (e.g., Kim 1999, Dutrenit 2000). In the increasing attention to knowledge, Archibugi and Coco (2005) arrange technological capabilities into three dimensions: embodied/disembodied knowledge, codified/tacit knowledge, and knowledge generation/diffusion.

2.2.2.2 Stages of technological capability building

More specifically, the building of latecomers' technological capability occurs through the technological trajectory that follows a reverse product life cycle (PLC) (e.g., Katz 1987, Kim 1997a, Hobday 1998a, Dutrénit 2000) (Figure 2.2).

Duplicative imitation stage: Latecomers commence technological capability building by acquiring and assimilating existing mature technologies from advanced countries. Manufacturing productivity is initially lower than in forerunner competing firms because of the higher learning cost associated with the early stage (Khan and Blankenburg 2009). However, if their learning is successfully adaptive to the technologies acquired (i.e., if technological assimilation occurs), latecomers eventually achieve an even lower marginal cost and have a cost advantage in the global (low value-added) market (*ibid*).[13] This process is driven by learning by doing and using as the 'by-products' of the daily production activities (Lundvall and Johnson 1994).

Creative imitation stage: Latecomers attempt to upgrade their technological and market position through the acquisition of more sophisticated technologies and strengthening of in-house R&D (Kim 2001b). In the intermediate stage of technological accumulation, they try to design their own products, aiming to improve existing foreign products. However, this is not innovative; these are 'facsimile products' with improved performance (Kim 1999). Learning by searching becomes important as a type of 'intentional learning' (Lundvall and Johnson 1994) at this stage.[14]

Innovation stage: Latecomers eventually reach the innovation stage. At this point, technological and scientific knowledge are generated on their own. They are in direct market competition with forerunners based on innovative products – either by adding new features or functions and architectural innovation, or by creating further radical innovation-based products (Figure 2.2). Distant searching and learning become critical at this stage. Accordingly, uncertainty and cost of learning by (more distant) searching sharply increase compared to the previous stages, especially in science-intensive technology.

[13] Moreover, the absolute labour cost is much lower than in advanced countries (*ibid*.).
[14] In terms of learning costs and market competition, they lead again the same cycle seen with the initially higher learning cost but it has a gradual achievement of lower marginal cost and then penetration to the global market. Hobday (1997, p.32-33) stresses the deliberate effort and investment of technological learning as the manner of willingness rather than the simple learning-by-doing as a passive form.

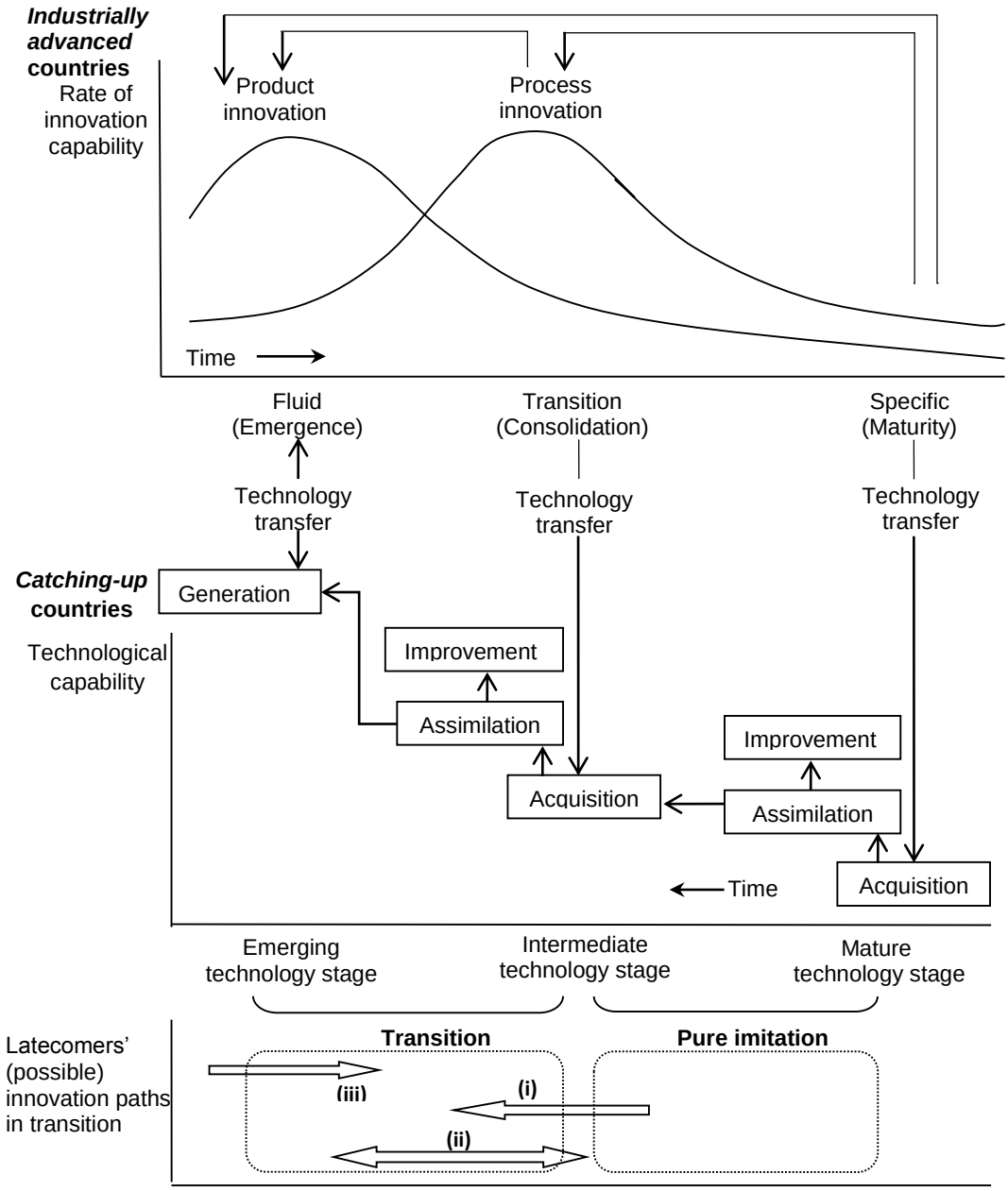

Figure 2.2: Technological catch-up trajectory

Source: Minor modification of Kim (1997a, p.89) and Song et al. (2006)

2.2.2.3 Driving forces of technological capability

The stage model of technological capability is constructed based on an operational capacity concept, absorptive capacity. An increase in absorptive capacity drives the latecomer to move up in position towards the more creative imitation and innovation stages. Absorptive capacity was originally defined by Cohen and Levinthal as a firm's ability to effectively internalise external knowledge sources for innovation activity (1990).[15] On the one hand, the existing knowledge base and its further accumulation act

[15] In their term, the ability to 'recognise the value of new, external information, assimilate it, and apply it to commercial ends'.

as a foothold to absorb external knowledge effectively (i.e., they increase absorptive capacity) (Kim 1997b, 1999).[16] On the other hand, when the new knowledge base that a firm is eager to acquire is different from the current knowledge base and R&D, the firm needs to deliberately generate absorptive capacity apart from the current R&D (Cohen and Levinthal 1990).[17]

2.2.2.4 Technological capability in the transitional phase

Once latecomers begin to transition from the imitative production stage to the innovative development stage, they face increasing uncertainty in both technological knowledge and environmental conditions, as recent studies have shown (e.g., Dutrénit 2000, Hobday et al. 2004, Kale 2005). Thus, confronting tasks needed for transition involves a broader scope and new kinds of learning, both technological and non-technological. In line with this, returning to Bell and Pavitt (1997), this research approaches technological capability in transition as a change-generating dynamic capability that leads to reconfiguration of their imitative learning pattern and resource operation and adaptation to environment change.[18] That is, the research conceptually treats the technological capability building as a transitional learning process of latecomers towards more distant searching and learning.

2.2.3 Micro-dynamics of innovation: organisational learning

Bell and Pavitt (1995) emphasise that technological capability encompasses both the accumulation of technological knowledge and the development of corresponding organisational factors. The organisational perspectives can be seen in the concept of organisational learning.

2.2.3.1 Definition

Organisational learning is theorised to represent interactive learning between organisational members, given environmental change (e.g, Cyert and March 1963, Simon 1969, March and Olsen 1975, Argyris and Schön 1978, Miles and Snow 1978, Duncan and Weiss 1979, Fiol and Lyles 1985). The interaction can be expressed as a

[16] I.e., problem-solving activity through dynamic knowledge conversion and interaction between members.
[17] Absorptive capacity is automatically accumulated as a 'by-product' of firms' current R&D if they carry out future innovation activity around their present knowledge area (Cohen and Levinthal 1990)
[18] Dynamic capability is defined as 'the firm's ability to integrate, build and reconfigure internal and external competences to address rapidly changing environments' (Teece et al. 1997). In particular, the concept of dynamic capability stresses change processes by reconstituting existing structures of business and resource combination (Helfat et al. 2009: p.29). At the extreme, even though firms have the same kinds of resources, they express differentiated competitive advantages because of the diversity of their ability to conduct these tasks using the same resources. That is, resources are transformed into 'firm-specific assets' that connote the nature of inimitability and heterogeneity. Several theoretically similar definitions corresponding to the dynamic capabilities within the resource based view have been introduced, such as core competencies and knowledge-based view of the firm (Prahalad and Hamel 1990, Grant, 1996).

sequential interaction, a socialising process or a collective action process that facilitates the adaptation of individuals and organisations to an environmental change.[19]

Through this process, an organisation stores individual knowledge collectively over time, and in turn, builds its own identity that influences the learning pattern of individual members (Nelson and Winter 1982, Simon 1991). An organisational routine emerges, carved out by all organisational members over time (Cyert and March 1963, Simon 1997, Feldman and Pentland 2003, Becker et al. 2005).[20] In turn, the strength of the organisational routine affects the retention of a certain type of organisational learning (Simon 1991).[21] Core capability (Leonard-Barton 1995) is formed in this process of routinisation.[22]

Routinisation, on the one hand, can lead to a virtuous circle of a series of routines over time by refreshing organisational memory, acting as a source of organisational flexibility for change (Feldman and Pentland 2003, Becker 2004). On the other hand, excessive routinisation of a specific organisational learning pattern can create organisational inertia. In this case, organisational capability at a given time is transmuted to organisational rigidity at a later point in time (Leonard-Barton 1995).

Thus, the key issue, in view of dynamic capability, becomes the proactive preparation and timely establishment of proper (alternative) organisational learning patterns. With respect to latecomers' transitions, the task faced is distant searching and learning patterns must be established to build innovative technological capability, overcoming the proximate organisational learning routine for imitation.

Relatedly, Kim (1997a, pp. 4-6) describes technological capability as 'the level of organisational capability' at a given point in time. Because of the dynamic nature of the transition, this research sees technological learning as conceptually equivalent to organisational learning, which more explicitly exposes the strategic and organisational

[19] As Nonaka and Takeuchi (1995) noted, knowledge conversion between codified and tacit knowledge is processed through these interactive mechanisms.
[20] It is originally defined as parts of organisational activities that have been carved into an organisation through repetitive action, such as human habits, and are thereby implemented without supervision and directions (Stene 1940).
[21] Interestingly, wear of the organisational memory has two sides that have positive and negative influence on the organisation (Simon 1991). On the one hand, useful knowledge learned by individuals within an organisation can gradually slip from organisational memory as the personnel are substituted over time. On the other hand, the timeworn, and therefore irrelevant, knowledge for the present organisational learning can be positively eliminated from the organisational memory.
[22] Thus, organisational learning has three kinds of nature: routine-based, history-dependent, and target-oriented (Levitt and March 1988). By virtue of this nature of organisational learning, an organisation can be identified as an independent evolutionary entity over time, displaying inimitability and heterogeneity in dealing with resources.

dimensions in a firm's technological capability building. Hereafter, technological learning is considered interchangeable with organisational learning.

2.2.3.2 Exploitation and exploration

Related to these transitions, two different modes of organisational learning are identified in the literature on organisational theory: **exploitation** and **exploration** (e.g, Argyris and Schön 1978, Miles and Randolph 1980, Shrivastava 1983, March 1991, Crossan et al. 1999, Benner and Tushman 2003, Gilsing and Nooteboom 2006, Gupta et al. 2006). Exploitation involves 'reactive' and 'single-loop' learning based on existing rule-based error correction processes. Production, refinement and efficiency are involved. By contrast, exploration indicates 'proactive' and 'double -loop' learning that leads to rule and pattern changes. Risk-taking, discovery, experimentation, variation and unlearning are involved. Therefore, the two modes of organisational learning have different goals (March 1991): 'the use and development of things already known' versus 'a pursuit of new knowledge' (Levinthal and March 1993, p. 105).

In terms of technological learning, the technologies in use at a given time come from two search processes: 'the search for refinement' and 'the search for innovation' (Levinthal and March 1981). The search for refinement is aimed at fine-tuning and economising existing technologies for efficiency, and thus it indicates exploitive learning. The search for innovation involves developing new and improved technologies; it indicates exploratory learning.

In this context, short-term competitive advantage mostly relies on exploitive learning, whereas exploratory learning is necessary to sustain a firm's longer-term competitive advantage. Thus, the two modes of learning are mutually complementary for the survival and growth of a firm. In addition, it should be noted that these types of learning are two different phases that are linked to each other during the learning cycle, which moves from an initial search for problems to problem solving, and then on to improvement of solutions. The degree of exploration and exploitation, and the proportion of learning that is focused on each of the two modes will vary depending on the external and internal situation of each firm. As March (1991, p.72) points out, 'The evolutionary dominance of an organisational practice is sensitive to the relation between the rate of exploratory variation reflected by the practice and the rate of change in the environment'.

2.2.3.3 The vulnerability of exploratory learning

Mutual exclusivity between the two modes of learning occurs when there are limited resources available within a firm and there is resource competition between exploitative and exploratory learning (March 1991). Thus, a firm must decide whether to focus on exploitation-oriented or exploration-oriented learning, and how many resources should be allocated to each route (*ibid.*).

Often, this mutual exclusivity leads to the intensification of exploitive learning, encroaching on developing long-term competitiveness through exploratory learning (*ibid.*). The return from exploitive learning can be realised in a stable and predictable way based on its involvement primarily with refinement and improvement of existing technologies and routines. On the contrary, the expected return from exploratory learning is relatively uncertain ('distant' and even frequently 'negative') because of its engagement with novelty, experimentation and discovery (*ibid.*).[23]

Thus, the adaptive process of exploitive learning is much easier than that of exploratory learning, and may lead to an over-focus on present goals, profits and capabilities, even when firms are faced with environmental change (He and Wong 2004). When excessive exploitive learning occurs, it lessens the opportunities for initiating or continuing exploratory learning, leading to a competency trap (Levitt and March 1988, March 1991).[24] This has been referred to as 'vulnerability of exploration' (March 1991) and 'the myopia of learning' (Levinthal and March 1993).[25]

In brief, the difficulty of carrying out both types of organisational learning in balance can be attributed to limited resources available to the firm and excessive routinisation. Exploratory learning can be continuously operated by guaranteeing the autonomy of exploration-conducting sub-units, acquiring the support from senior management and overcoming organisational inertia (Benner and Tushman 2003, O'Reilly and Tushman 2008).

2.2.3.4 Exploratory learning in the transitional phase

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[23] If the returns from the two modes of organisational learning can be rationally calculated and compared, then the allocation of resources available to an organisation will be rationally conducted. However, the relatively higher predictability of calculating the return from exploitive learning, and conversely the relatively lower predictability of estimating the return from exploratory learning, increases the difficulty of the firm's decision as to whether it will choose exploitation or exploration to build and sustain its competitive advantage. Thus, basically it would be natural for an organisation with bounded rationality to be inclined to choose exploitive learning.

[24] In this context, the present core capabilities are deteriorated to core rigidities within a certain time frame (Leonard- Barton 1995).

[25] Conversely, excessive exploratory learning in an organisation in which the exploration is routinised can also destroy the organisation because of on-going negative profits from the excessive exploration.

The literature on the two modes of organisational learning mainly considers the trade-off between them, and the dilemma this creates for innovating firms. For forerunners, the main task comes in monitoring and learning new technologies through exploratory learning while also maintaining technological dominance in established technological areas through exploitive learning – that is, ambidexterity. Ambidexterity refers to creating a 'balance between the needs of today's innovation demands with that of tomorrow's innovation possibilities' (Tushman et al. 1997, p. 6). Some have argued that organisational ambidexterity is the root of the dynamic capabilities of firms (Benner and Tushman 2003, O'Reilly and Tushman 2008).

However, in a latecomer context, the key task may not be balancing these two modes of learning. Instead, it is likely to involve the reinforcement of a pattern of exploratory learning while casting off the learning associated with exploitation that had dominated during the imitation stage. A fundamental feature of this transitional phase involves developing technological learning associated with 'new to the market' innovations that goes beyond the previous focus on 'new for the firm only' innovations. A higher amount of exploratory learning is necessary to allow the firm to search for more novel processes and products. In research on the KoPI, it is therefore important to examine how the exploratory mode of technological learning has been enhanced as the industry has tried to develop new drugs and move beyond the production of generic copy drugs.

Overall, the contrasting features of different learning patterns associated with exploitation and exploration provide a conceptual lens for understanding the changing patterns of latecomers' technological learning during the transitional phase, which involves the initial building of new innovative capability. As a consequence, this research has adopted a slightly different approach from previous literature, which tends to focus on ambidexterity. It instead focuses on the establishment of a highly explorative mode of technological learning. Lastly, it should be noted that the two modes of learning are graduated rather than dichotomised concepts; in any given learning cycle, there can be various degrees of exploitation and exploration.

2.2.4 Macro-dynamics of innovation: innovation systems

While the micro-dynamics of building technological capability in transition are conceptualised through changes in a firm's organisational learning, the macro-dynamics can be understood through a systemic approach to innovation (e.g., Freeman 1987, Carlsson and Stankiewicz 1991, Lundvall 1992, Nelson 1993, Carlsson 1995, 2002, Breschi and Malerba 1997, Cooke et al. 1997).

Edquist (1997, p. 13) quoted Fleck's (1992, p. 5) definition of a system: 'complexes of elements or components, which mutually condition and constrain one another, so that the whole complex works together, with some reasonably clearly defined overall function'. In line with this, an innovation system 'is constituted by elements and relationships that interact in the production, diffusion and use of new, and economically useful, knowledge' (Lundvall 1992, p. 2). No single actor can create, disseminate and apply necessary knowledge for innovation on its own; thus, the concept of an innovation system considers interactive learning among actors (e.g., Lundvall 1992, Nelson 1993, Edquist 1997).

The concept is particularly useful in understanding the relationships between innovation elements and their interactive learning patterns. Innovation actors can be classified into primary and secondary types (Liu and White 2001). Primary actors are real performers that conduct innovation activities such as R&D, production, education and linkage (e.g., firms, universities, public research institutes, factories and consumers). Secondary actors (e.g., central and local governments and regulatory agencies) are in charge of guiding the behaviour of primary actors. Relational institutions guide the inter-actor relationships via means such as policies, industrial standards and an intellectual property rights (IPR) regime.

While most literature focuses on the structural establishment of innovation – that is, the roles of innovation actors and the formal linkages between them – there have been some studies that look at the function of innovation systems (e.g., Johnson 2001). Taking the second approach, Johnson (2001) divides the functional aspects of innovation systems into two categories: direct and supportive functions. Direct functions of Innovation systems work on identifying their problems, such as bottlenecks and functional failures, and solving them by creating alternative knowledge, such as new technology and products (*ibid.*). Supportive functions facilitate the direct functions by, for example, providing incentives for innovation actors or guidance in directing the search and stimulation of markets (*ibid.*). For example, the changed evaluation system of national R&D projects can be regarded as a supportive function to guide the direction of innovation activities.

2.2.4.1 National and sectoral innovation systems

This sub-section will review the concepts of the national innovation system (NIS) and the sectoral innovation system (SIS), because the transition of the KoPI has taken place under the influence of the national institutional setting and within the context of the pharmaceutical sector.

First, the NIS is generally defined as an innovation system for economic development, comprising diverse actors and institutional settings (e.g., Freeman 1987, Lundvall 1992). Actors in the NIS include industrial firms (producers and users), public research institutes and the government. Institutional settings include S&T and industrial policies, rules and market mechanisms.

The concept of the NIS is built on the assumption that innovation patterns are different across nations, depending on the structural differences in production systems and institutional settings (Anderson and Lundvall 1997, Lundvall 1992). Structural differences include the 'internal organisation of firms', 'inter-firm relationships', 'the role of the public sector', 'institutional set up of the financial sector' and 'R&D-intensity and R&D-organisation' (Lundvall 1992, p. 14). For example, a highly integrated large firm-led economy and a network-led economy of smaller firms would have different patterns of innovation, and different modes of governance would be necessary to promote innovation generation and economic development (Anderson and Lundvall 1997).

Overall, the NIS provides a conceptual frame to illustrate the macro-level influence of 'the structural characteristics of a national economy such as its specific production structure, technical infrastructure, and other institutional factors' (Guerrieri and Tylecote 1997, p. 107) on individual actors' innovation performance.

On the other hand, the SIS considers the innovation pattern of specific industries. The concept shares the underlying frame of the NIS – collective learning for knowledge generation and diffusion among diverse innovation actors and the influence of institutional settings on innovation. Malerba suggests that there are seven key elements of an SIS: products; market and non-market actors; knowledge and learning processes; basic technologies, inputs and demands and their linkages and complementarities that comprise a sector's scope; interactive processes within and without external firms; competition and selection processes; and institutions (2002).

These elements differentiate the conceptual focus of the SIS from that of other innovation systems in two respects. First, the SIS deals more directly with the product, its market and its competition. Second, the SIS considers the relationship between the sector-specific knowledge base and the institutional and national factors surrounding the industry (McKelvey et al. 2004). The sector-specific knowledge base is interpreted in the context of the technological regime of a sector.

The technological regime consists of the characteristics of knowledge, cumulativeness of knowledge, and opportunity of innovation and its appropriability (Breschi and Malerba

1997). It is an underlying knowledge dynamic that affects 'the nature of problems firms have to solve', 'the type of technological learning', the structure of incentives and 'the basic processes of variety, generation and selection' (Malerba 2002, p. 250). In other words, each industry has distinct interactive and competitive relationships and organisational boundaries in creating innovation, depending on its technological regime (Breschi and Malerba 1997).

In the latecomer context, an industry in the transitional phase encounters a changing technological regime because the industry shifts from being imitative (based on knowledge exploitation) to being innovative (based on knowledge generation). Moreover, a new core technology's penetration into a sector such as biotechnology also requires the reconfiguration of the SIS, that is, the interactive pattern of innovation actors and institutional settings must change to deal with the new knowledge dynamics.

2.2.4.2 Innovation systems in the transitional phase

While innovation systems are used in this thesis as the main analytical framework to understand the innovation structure of the KoPI, capacity/capability-based (more prescriptive) interpretations of innovation systems are also drawn upon. For example, the national technological capabilities suggested by Lall (1992), the national learning system by Viotti (2002) and X-efficiency of the NIS by Niosi (2002), all have to do with the capability view of the NIS, which includes the effective constellation of innovation elements and the efficient allocation/reallocation of resources to embedded actors and their interlinks. With respect to latecomers' transitions, the key issue of system-level dynamic capability becomes how effectively institutional and country-specific factors are reconfigured to cope with changing knowledge and to promote the embedded actors' exploratory learning.

2.3 Technological Capability in the Transitional Phase

The following two sections look into two areas of literature that are contextually related to the transition of the KoPI: industrial catch-up, including the transitional phase, and science-based innovation. To begin, this section reviews the common features of a successful catch-up in Asian NIEs, and the main issues that occur during a transition. It goes on to look at the firms' technological learning and innovation systems.

2.3.1 Micro-level dynamics

2.3.1.1 Features of rapid catch-up

There are two underlying drivers that enable stepwise technological capability building in latecomer Asian NIEs[26]: enhanced absorptive capacity in reversing the PLC and active participation in the global production network. Both of these drivers involve establishing a virtuous cycle between technological catch-up and market catch-up.

Absorptive capacity is regarded as a main factor conditioning the rate of latecomer firms' technological catch-up. In empirical studies, absorptive capacity in technological catch-up is often explained using the cases of Samsung and Hyundai (e.g., Kim 1997b, 1998, Mathews and Cho 1999, Lee 2000). In particular, Kim (1997b, 1998) emphasises that technological learning is a function of a firm's absorptive capacity, which consists of two elements: upgrading the prior knowledge base and an intensified learning effort.

The literature shows that Korean latecomer firms' rapid market catch-up is realised by active participation in the global production network. Pack (2000, p. 72) highlights the importance of exports in the catch-up of Asian NIEs as follows: 'Export growth became the standard by which all policies were judged, including those that provided initial protection for infant industries'. Furthermore, the export-led catch-up by Korean latecomers seems to intensify as they move up to become innovative learners.[27]

In industrial practice, a model combining original equipment manufacturing (OEM), own design and manufacture (ODM) and own brand manufacture (OBM) (Hobday 1995, 1998a) clearly shows the mechanism of building virtuous cycles between technological and market catch-up, particularly in consumer electronics by Samsung and PCs by Acer (e.g., Hobday 1998a).

The initial stage of catch-up relies on buyers' advanced technological and marketing capabilities. OEM contracts led Korean and Taiwanese latecomer firms to build production capability and use foreign buyers as export channels with minimum marketing costs. The latecomer firms then quickly moved to design and develop their own imitative products based on enhanced absorptive capacity and technological guidelines from the buyers. These activities are referred to as ODM in the creative imitation stage. From this stage, companies face increasing difficulty in receiving technology transfers, as

[26] Main literature used: Kim 1980, Hobday 1995, Chen and Sewell 1996, Ernst 1998, 2000, Ernst and Guerrieri 1998, Mathews and Cho 1999, Choung et al. 2000, Mathews 2002.

[27] For instance, overseas sales for Samsung Electronics and Hyundai Motors accounted for 83% of their total sales in 2011. In addition, LG Electronics also took 85% and Kia Motors took 80% (Money Today 2/2/2012). Of course, the proportion does not mean the total proportion of net export because the figure includes overseas production.

advanced firms start to recognise the latecomers as potential challengers. Finally, the latecomers begin to design their own products and compete directly with advanced firms. These activities are called OBM in the innovation stage.

For example, Anam (now Amkor Technology), once the largest chip-packaging company in the world, followed the catch-up path from OEM to ODM (Hobday 1995). It entered the semiconductor business by receiving orders for simple assembly with technological support from a US company in the late 1960s. It then advanced to a sophisticated packaging stage with little technological support from overseas clients in the late 1980s, and then to new chip-packaging design and processing in the 1990s. The same pattern of incremental technological upgrade can be seen in the case of Hyundai, a Korean automobile company (Kim 1998). In the late 1960s, Hyundai started its business by assembling components from semi-knock-downs transferred from the Ford Motor Company. Hyundai succeeded in producing licensed cars in the 1970s and developed its first compact car with its own developed engine, Accent, in 1994.

At present, some of the Korean and Taiwanese latecomers in high-tech industries have successfully developed their own R&D and brands such as Acer, Hyundai, Samsung and TSMC. Overall, taking the long-term view from the outset of their business, they followed a similar stepwise catch-up path by building technological capability incrementally and exploiting the export market.[28]

2.3.1.2 Technological capability in the transitional phase

In response to the increasing presence of latecomer firms in the innovation stage, some recent literature has focused on the transition from the imitation stage to the innovation stage (e.g., Dutrénit 2000, Hobday et al. 2004, Kale 2005). In the transitional phase, latecomer firms often face rising uncertainty in both technological learning and environmental conditions. They compete more directly with innovative rivals in more novel and complex product markets. Thus, latecomers must have the technological and non-technological capabilities to deal with the change. Ways to do so include deepening a company's current knowledge base and extending to a new knowledge area, identifying the changing characteristics of the catch-up environment in the market and in institutions, building or reorienting strategic goals, searching for alternative methods and reorganising resources. The goal of these actions is to upgrade imitative capability to

[28] The following remark symbolises some latecomers' leapfrogging: "Rudely pushing the Japanese aside are South Korea's Samsung, LG and Hynix. Nor, is it only and electronics phenomenon. In the auto industry South Korea's Hyundai/Kia Motors…The same goes for shipbuilding and even soap operas where the Korean shows are even all the rage in Japan" (Prestowitz 2012).

innovative capability in a timely manner. In other words, the dynamic nature of a latecomer's technological learning emerges in the transitional phase.

Three main approaches for understanding transition are identified in the literature, all of which are related to one another: a) strategic complexity in dealing with the transitional phase, b) the need to build dynamic capability and c) the variety of technological catch-up paths in the transitional phase.

a) Strategic complexity in dealing with the transition phase

Hobday et al. (2004) analysed 26 innovation-seeking Korean firms and found two types of complexity in their transitional phases. On one hand, developing OBM products requires technological learning itself to become more explorative and complex. On the other hand, non-technological catch-up factors become more complicated, such as the relationship with buyers (often as industrial leaders) and the structure of market competition.

Specifically, latecomers try to secure a market return through their imitative products for OEM/ODM. At the same time, they also try to develop more innovative. In the transitional phase, one potential risks is competition in the OBM market with the companies that buy their ODM/OEM products (*ibid.*). That is, latecomers are forced to deal with competitive and collaborative relationships with the forerunners, such as continuous subcontracts and more horizontal competition.

In dealing with strategic complexity, some Korean and Taiwanese firms attempt to take a dual-portfolio strategy, becoming what are known as hybrid firms; they may operate both leadership and 'followership' strategies, depending on the degree of innovation in each product line (*ibid.*). Some products are developed for OBM, while others are developed as ODM or OEM. Regardless of its final success, this dual strategy can be seen as the strategic response of latecomer firms to adapt to the changed technological and market environment in the transition.

b) The need to build dynamic capability

Latecomer firms cope with the strategic complexity of the transitional phase by building dynamic capability. Some studies have identified substantial features of latecomer firms' emerging dynamic capability, such as combinative capability, latecomer absorptive capacity and embryonic strategic capability (e.g., Mathews and Cho 1999, Chuang 2010, Dutrénit 2004). These features can be seen as ways of upgrading latecomer firms' technological capability to cope with a more dynamic technological and competitive environment.

Combinative capability (Mathews and Cho 1999) stresses the ability to rapidly assemble imported technologies, enabling further speedy resource uptake and rapid entry to the new generation of products. That is, combinative capability is the competence platform for moving up to more advanced product versions. The enhancement of combinative capability is exemplified by Samsung's rapid mastery of product generations in dynamic random access memory (DRAM), especially its development of the world's first 64M DRAM. Latecomer absorptive capacity (Chuang 2010) is the learning platform to quickly expanding high-tech product fields towards other product categories. An example of using latecomer absorptive capacity is the Taiwanese firms' entry to the LCD business based on their existing specific technological bases in PCs and semiconductors.

While these two kinds of absorptive capacities concentrate on the technology-centred dynamic learning process in transition, embryonic strategic capability (Dutrénit 2000, 2004) focuses on the managerial and organisational complexity of technological capability building in the transitional phase.[29] The concept of embryonic strategic capability focuses on the latecomer firm's primitive strategic capability to drive forward to build more internal innovative capability and create a complex knowledge base.[30] Thus, this concept involves the initial establishment of an internal knowledge base in a specific technological area beyond a company's capacity to borrow and imitate (Dutrénit 2000). Embryonic strategic capability emphasises the organisational mechanism of technological learning, such as knowledge management, due to unseen complex learning processes (Dutrénit 2004).[31]

As they face the transitional phase, latecomers require technological and non-technological capabilities that are different from those needed in the imitation stage. Their knowledge base should become broader and deeper as their surrounding environment becomes more competitive and dynamic. The organisational process of technological learning also becomes more complicated.

c) The variety of technological catch-up paths for transition

The third approach to understanding transition relates to the variety of catch-up paths for moving beyond the transitional phase. Whereas the early catch-up stage (that is, the

[29] This is based on her earlier empirical work on large Mexican glass manufacturing companies (Dutrenit 2000).
[30] The innovative technological capability to "build, nurture, and renew strategic capabilities" (Dutrenit 2000) involving an innovation stage.
[31] The ultimate strategic capability, by innovative firms, involves the management of all technical-functions needed to deal with the changing environment. In this context, the organisational capabilities for managing complex strategic assets are highlighted in much of the strategic management literature dealing with this issue (Dutrenit 2004).

duplicative imitation stage) is commonly initiated by learning simple production technologies by drawing on external technologies, the literature reflects an increasing variety of paths for further catch-up in the transition phase.[32]

Three possible paths for overcoming the transitional phase can be identified through observing recent information and communications technology (ICT) products and systems developed in Korea (Choung et al. 2014, Song et al. 2006): (i) the development of more innovative products that advance the reverse PLC, (ii) the architectural differentiation of the product entering just after fixing a dominant design, and (iii) the development of innovative products prior to establishing a dominant design (see the third image in Figure 2.2).

For example, Samsung's DRAM business successfully overcame the transitional phase by intensifying process innovation along the reverse PLC, that is, path (i) (Choung et al. 2014). Some Korean firms follow innovation path (ii), which is known as architectural differentiation (*ibid.*). MtekVision and Core Logic, developers of camera control processors (CCPs) and camera application processors (CAPs) for mobile phones, quickly entered the camera phone market just after the dominant design of the mobile camera phone was established in 2002. Through joint R&D with mobile phone manufacturers such as LG and Samsung, they were able to change the interface between the system (mobile handset) and component (camera module) to enhance image processing.[33] In particular, Song et al. (2006) suggest the technological path has high potential for latecomers' transitions with no need to develop novel technologies on their own. In fact, this architectural differentiation underlies the recent trend of R&D in Korea focusing on the convergence of ICT products.

Similarly, Forbes and Wield (2000) argue that latecomers may enjoy the benefit of followership when they enhance innovative design capability based on dominant technologies. This design capability enables latecomers to maintain a very small gap with forerunners, a distinctive form of competitiveness. Although they do not refer to architectural innovation, the authors clearly suggest the value of followers' design capability for architectural innovation based on existing technologies.

Innovation path (iii) is more radical. Latecomer companies on this path focus on developing innovative products prior to the establishment of a dominant design (Choung

[32] For example, in the ODM stage, the different catch-up paths among Asian NIEs become apparent. Taiwanese electronic companies focus on deepening specialisation in the ODM, while the Korean Chaebol try to jump to the OBM stage with vertical integration in parallel with ODM contracts (Hobday 1995).
[33] Joint R&D also led to the simultaneous development of the system and its components (ibid.).

et al. 2014). However, in practice, latecomers engaging in radical innovation often fail. In 2005, the world's first commercialised mobile TV technology, digital multimedia broadcasting via terrestrial transmission (T-DMB), failed to find a market in Korea. The cause was a lack of institutional capability on the part of latecomer firms and the government to establish global technology standards, create an early-stage market and coordinate diverse innovation actors (*ibid.*).

Lee and Lim (2001) similarly lay out three different technological paths that latecomer firms can take to accelerate the transitional phase: path-skipping, path-creating and path-following technological capability building.[34] First, a few Korean firms successfully carried out a transition phase by skipping the intermediate learning stage, instead using emerging technologies from outside the company. For example, at one time, a carburettor-based engine was the dominant design in the automobile industry. Instead of mastering the dominant technology, Hyundai focused on learning about the new electronic injection-based engine from foreign developers and thereby narrowed the gap in its engine technology.

Other Korean companies moved beyond the transition stage by developing new technologies, such as the world's first commercialisation of a code division multiple access (CDMA)-based mobile communication system. By doing so, they skirted the then-dominant communication systems, such as the time division multiple access (TDMA)-based global system for mobile communications (GSM) in Europe and the analogue system in the United States.[35]

The opportunity of latecomers to exploit a new technological paradigm (Perez 1985) is a critical driver for creating a new path of development. Lee et al. (2005) argue that Korean TV manufacturers were able to overtake their Japanese forerunners by swiftly changing the technological focus to the emerging technology of digital TV, away from the incumbent-led analogue TV.[36]

Lastly, it is worth considering the underlying motive of the varied catch-up paths. Regardless of the kinds of paths latecomers take, each path reflects their effort to search for routes that rapidly reduce the gap with frontrunners. Hobday (2005) suggests that latecomer firms have to consider a way of substituting deficits in technological and

[34] Three different paths are also based on the consideration of the differences in each industry's technological regime and their influence on latecomers' transitions.
[35] Meanwhile, the Korean electronic *Chaebol* also was strengthening technological capability in its conventional catch-up path in consumer electronics.
[36] As stated, the rapid technological shift is also based on combining with the prior accumulated complementary asset such as the experience of TV production, i.e., the importance of absorptive capacity.

marketing conditions, which are shaped by earlier movers. The manner in which they do so can be seen as a major factor in producing a variety of catch-up paths (*ibid.*).[37] In line with this, the ways of substituting the preconditions and formulation of own catch-up paths should consider different national, sectoral, and resource conditions (Hobday 2003, 2005, 2011). Hobday's argument is based on adopting Gerschenkron's model, which is the complementary substitution of missing prerequisites for economic catch-up depending on each country's circumstances:

> In Gerschenkron's model…only by choosing and successfully following distinctive paths (and therefore stages) of development can latecomer nations meet the new circumstances presented to them by the actions of earlier developers (cited in Hobday 2003, p. 295).

Overall, the variety of catch-up paths reflects increasing variation across latecomer firms in searching for more suitable ways of building the technological capability concerned with the complicated technological and market dynamics in transition. The argument for the complementary substitution of missing prerequisites can guide latecomers who are searching for their own catch-up paths.

2.3.1.3 Changing nature of technological learning

A latecomer firm's rapid catch-up is framed within a stepwise catch-up model, composed of enhancing absorptive capacity in technological learning coupled with export market performance. In this general framework, recent literature extends the focus to the complication of latecomers' technological learning in the transitional phase.

The recent literature further shows that latecomer firms face less favourable and more competitive market environments in the advanced catch-up stages, especially in their relationships with leading incumbent firms. In addition, the attempt to develop innovative products itself imposes more complex and distant technological learning on latecomer firms. That is, the literature describes the discontinuous characteristics of the technological learning pattern between the previous imitation stage and the advanced catch-up stage. Specifically, latecomers in the transitional phase must overcome technological and market conditions and rules, often shaped by the earlier movers.[38]

[37] For example, the catch-up by Samsung is exemplified as the strategic outcome of forming own catch-up path considering barriers and advantages of technological and marketing sides as a latecomer.

[38] However, this does not mean that surmounting the conditions/rules established can be achieved only through direct competition with the forerunners.

Because of these challenges, the change of the technological learning pattern in transition becomes a critical issue. Hobday et al. (2004) suggest that there is a need for latecomers to sustain research activities through structural, behavioural and managerial flexibility. This suggestion is in line with the so-called anti-routine view of innovation (Hobday 2005), which holds that innovation occurs when routinised imitative learning patterns become innovative learning patterns. Whether latecomer firms can build dynamic capability for transition has to do with the change-generation of the imitative learning pattern.

Recent studies have addressed some problems that occur in changing the learning pattern from imitation to innovation. Lee and Lim (2001) briefly mention that Hyundai prevented the penetration of an imitative learning routine into its first engine development project by establishing a new R&D centre. Kale (2005) reveals the difficulty in changing individual researchers' approaches when trying to move from generic drug development to new-drug R&D in Indian pharmaceutical firms.[39] These examples show that latecomers need to find effective ways of strengthening the exploratory mode of technological learning for transition.

However, in general, the literature has addressed the pattern change in latecomer firms' technological learning only in a limited way, and mostly concentrates on a few *Chaebol*-led and engineering- or technology-driven catch-up industries, as shown earlier. The dynamics of transition and the technological learning pattern in the science-based pharmaceutical industry remains an overlooked area.

2.3.2 Macro-level dynamics

2.3.2.1 Features of institutional conditions

Other literature on catch-up focuses on the institutional influences in industrial catch-up (e.g., Freeman 1987, Westphal 1990, Amsden 1991, Lall 1994, Mowery and Oxley 1995, von Tunzelmann 1995, Kim 1997a, Ernst and Guerrieri 1998, Wong 1999, Viotti 2002, Mazzoleni and Nelson 2007, Maio 2008, Khan and Blankenburg 2009). These studies illustrate that Asian latecomer firms' rapid catch-up occurs not only through their own efforts, but also by institutional conditions. The common institutional features that led to successful industrial catch-up are summed up in the three macro-level conditions identified by Mazzoleni and Nelson (2007): a) ample flow of human resources between the catching-up and advanced countries, b) strong governmental support, such as R&D

[39] His study seems to be the first research that apparently raises the issue of 'learning' and 'unlearning' in latecomer pharmaceutical firms.

investment and various incentives, and c) loose operation of an intellectual property rights (IPR) system.

Ample flow of human resources

Koreans with overseas training and PhD holders who returned to local Korean companies such as Samsung are a critical factor that strengthened absorptive capacity (Kim 1997b). Similarly, formal and informal networking between local Taiwanese companies (e.g., Acer) and Taiwanese engineers in technologically advanced regions (such as Silicon Valley) provided a channel of technological learning that fostered the Taiwanese computer industry (Kim and von Tunzelmann 1998, Ernst 2000).

Governmental leadership and industrial policies

The successful catching-up countries (the US, Japan, Korea and Taiwan) were active in the use of industrial policies to protect and foster infant industries, especially target industries (Mazzoleni and Nelson 2007). Biotechnology is the most recent case of a targeted sector in Asian NIEs. In the literature on Asian NIEs,[40] governmental leadership is actualised in two institutional dimensions: strengthening national absorptive capacity, and market creation through domestic market protection and export support.

To strengthen national absorptive capacity, the main institutional actions taken were to concentrate on the establishment of necessary innovation elements, such as the supply of qualitative human resources and the establishment of GRIs as the mediators of technology acquisition and diffusion.[41] As some latecomer countries deepen the transitional phase, national support since the 1990s has extended to fostering research-oriented universities and technology-intensive start-ups. Such institutional elements can be seen as a national resource commitment for promoting active technology absorption (Viotti 2002).

Market creation can occur through industrial policies linked with trade policy. In general, the Asian NIEs instituted various performance-based incentives for efficient national resource management, such as direct and indirect subsidies for R&D, high entry barriers to the domestic market such as tariffs and regulations, procurement and export support through financing, and focusing on targeted industries (Lall 2000). From a macro-level

[40] It is often compared with other regions' catching-up processes and performance (e.g., South America).
[41] GRI – e.g., ITRI (Industrial Technology Research Institute) in Taiwan and KIST (Korea Institute of Science and Technology).

view, these incentives were intended to actualise an industrial policy that combines export-oriented industrialisation (EOI) with import-substituting industrialisation (ISI).[42]

By linking technological and market-side industrial policies, Korea and Taiwan were able to couple upgrading absorptive capacity with profit creation within a relatively short period of development. Linking these policies can be seen as the institutional driver of the formation of stepwise catch-up cycles of duplicative imitation, creative imitation and innovation stages over the last 40 years.

Loose IPR regime

In the past, latecomers could access forerunners' technologies with loose IPR restrictions in the catching up period, as long as they did not encroach on the markets of advanced countries (Mazzoleni and Nelson 2007). Interestingly, licensing was considered a tool for creating economic profits through technological transfer rather than a means of aggressive IPR protection for forerunners (*ibid.*).

2.3.2.2 Innovation systems in transition

Some recent literature on Asian NIEs' innovation systems focuses on the changing institutional setting in the transitional phase. In general, this change can be thought of as the reconfiguration of innovation elements and their relationship, moving from a system of utilising external knowledge to a system of internally generating innovation source. Two interrelated perspectives on this institutional change occur in the literature: a) the successful transition of latecomers' innovation systems, and b) institutional rigidity and flexibility in dealing with the transitional phase.

a) Successful innovation system transition

Dodgson et al. (2008) discuss a morphological (structural) reconfiguration of the NIS, drawing on the Taiwanese case of transition from technology use to technology generation. They compare the network formation of the present burgeoning biotechnology industry with previous industrial cases of ICTs. While the industrial network of ICTs was established to exploit imported technologies and is thus capable of catching up, the biotechnology network was formed to create its own knowledge base led by domestic research institutes. The new establishment of science parks and intermediary agencies support this knowledge base creation. While the authors illustrate

[42] When the incentives provided to firms resulted in dissatisfactory performance in exports, the government retracted the incentives offered, and thus the inefficiency of allocating input resources could be eliminated. By contrast, South American countries have been open-ended in forming efficient incentive structures, in general (Westphal 1990).

the overall transition of the NIS, they also note that there is a lack of a cohesive network between innovation actors.

The emergence of Singapore as one of the top three Asian countries in aerospace technology (Matthews and Zhang 2010) is a substantial example of a successful transition of a latecomer SIS in a high-technology sector (Vertesy 2013).[43] There were several factors that led to a 'transition without interruption' of the industry (*ibid.*, p. 137). One of these was institutional capability – the government's guidance of the direction of industrial transition and support for relevant innovation elements. The Singaporean government strategically considered the participation of the high-technology industry's global value chain by focusing on a specific segment, that is, component supply and the field of maintenance, repair and overhaul (MRO). This specialisation strategy was strongly backed by active investment in infrastructure and local R&D, as well as incentives to attract foreign manufacturers. The stable management of the air force in a small independent country and its geographical advantage as an airline hub also underpinned the strategy of focusing on MRO (*ibid.,* pp. 127-128 and p. 135).

The other driver is the strong possibility of technological accumulation in the MRO field within a short learning period, compared with the aerospace industry in general. While aircraft manufacturers have long development cycles, MRO-related products and services have no need for long development times (*ibid.*, pp. 127 and 135).

Overall, this case shows an effective way of overcoming the transitional phase and establishing a competent SIS through a smart and flexible industrial policy (*ibid.*). Singapore strategically combined its prior technological capability accumulated in the pure learning stage of maintenance and repairs to meet small domestic demand within the context of an industry's changing global value chain. Therefore, it was possible to incrementally upgrade technology and make a smooth transition to market profit. In contrast, the aerospace industry in Indonesia, which attempted to develop its own aircraft based entirely on public support, struggled to penetrate the global market (*ibid.*).

b) Institutional flexibility/rigidity of innovation systems

Some literature provides a more problematic view of latecomers' reconfiguration of innovation systems toward knowledge creation. To begin with, Kim (2000) broadly describes the systemic transmutation of the imitative Korean NIS (K-NIS) into a barrier that delayed the transition to an innovation-generating NIS. The government failed in coordinating various policy activities in the transition. The *Chaebol* were seen as

[43] The other two countries are Japan and Korea (Matthews and Zhang 2010).

candidates for further restructuring. They were increasingly regarded as an obstacle to fostering small and medium enterprises (SMEs). The education policies intended to support industrial technology led to a lack of research capability in the universities. Moreover, in terms of organisational culture, the proliferation of a top-down style, bureaucratic and militaristic characteristics, and short-term efficiency prioritisation also contributed to the delayed transition.

Interestingly, the rigidity of the Korean NIS can be traced by the implicit criticism in comparative studies between Korea and Taiwan. Wang (2007) argues that Taiwan's transition is based on upgrading a 'neo-Marshallian network-based' collective learning system comprising SMEs, public research institutes, and multinational corporations (MNCs). In contrast, Korea's transition is based on the acceleration of '*Schumpeterian* scale-based technological development' led by a few large conglomerates (*Chaebols*) that are vertically integrated.[44] The preponderance of resource allocation into *Chaebols* and the lack of network-based technological learning are indications of the systemic rigidity of the Korean NIS. They make adoption of the Korean catch-up model difficult for other latecomer countries.

Wong (2005) uses the case of fostering biotechnology to identify a procedural problem in the Taiwanese transition. He argues that the emerging innovation network of biotechnology in Taiwan has evolved with a lack of 'cohesive collaboration' due to the failure of the coordinative function of the government. He stresses the need for qualitative change in the manner of governmental intervention in the transitional phase:

> Second, measuring the role of governments in promoting biotechnology innovation solely in quantitative terms, more or less intervention, is problematic when we consider that what has always mattered most in the developmental state model – and not just the East-Asian variant – are the types of interventions initiated by governments, and furthermore, how well these initiatives match up with specific political, economic, social, and technological imperatives…in understanding the transitional dynamics of the developmental state in Taiwan (Wong 2005, p. 185).

In an innovation system, qualitative change in government intervention is associated with the effective transformation of the innovation actors and their network, changing knowledge utilisation for indigenous knowledge-generating innovation actors and

[44] The Taiwanese structure seems to be particularly suggestive regarding the industrial structure of the KoPI led by SMEs, which is likely to be closer to that of Taiwanese major industries than that of Korea led by *Chaebols*.

networks. For example, the top-down style of governmental leadership, which is effective in facilitating imitative learning, is not suitable for the promotion of biotechnology innovation (Wong 2005). Instead, biotechnology innovation takes place in an increasingly pluralistic institutional context among non-state innovation actors embedded in a local private and global research network (*ibid.*).

Overall, the literature shows that a latecomer's NIS faces increasing institutional challenges during a transition.

2.3.2.3 Changing institutional conditions

Overall, the common institutional features of rapid catching up were reviewed in the frame of innovation systems. These features can converge in a streamlined institutional environment for industrial development, thereby leading to efficient and rapid national-level resource operations. Technological capability building has been led by selected private firms with institutional guidance from government.[45] *Chaebols* were formed in this circumstance. Little conflict of interest between the private and public actors and between different institutional contexts (e.g., between the industrial development and the welfare system) disturbed Korea's rapid industrial development.

Some recent literature covers emerging institutional issues identified in the transitional phase (e.g., Kim 2000, Wong 2005). This literature mainly focuses on macro-level structural changes of innovation systems towards the fostering of internal knowledge generation and cohesive industrial networks. Institutional rigidity is also suggested as a potential difficulty in the reconfiguring of innovation systems.

However, empirical analysis of the reconfiguration of innovation systems is still limited to a macro-level general interpretation and policy suggestions. That is, the micro-dynamics of the change, such as the impact of S&T policies on technological learning practices, have rarely been addressed, particularly in the context of science-based industry in Korea.

2.4 Nature of Innovation in the Pharmaceutical Industry

This section reviews the distinctive dynamics of knowledge that underlie science-driven innovation in the pharmaceutical industry.[46] Three major features are discussed. First,

[45] The boundary of technological learning between the private and public actors has been fairly clear.

[46] The literature domains of science-based industries seem to be dispersed across other literature domains, such as public S&T policy, public and private R&D collaboration, the IPR regime and sectoral-specific areas (ICT, the pharmaceutical industry, biotechnology and nanotechnology). This review approaches the more general context of science-based industries rather than serving as a pharmaceutical industry-specific

the institutions and mechanism of innovation generation that establish science-based industries are described (Sub-section 2.4.1). Second, the emergence of biotechnology, which is often regarded as the substitutive technological paradigm for chemically synthesised drugs, is discussed (Sub-section 2.4.2). Third, the integral product architecture of drugs is reviewed and compared with modularity-based industries, which are most of the major catch-up industries in Korea (Sub-section 2.4.3). On this basis, the last sub-section (Sub-section 2.4.4) discusses the influence of these three features of knowledge dynamics on R&D trends in the pharmaceutical industry.

2.4.1 Science-based innovation

2.4.1.1 Basic institutions

There are a few noticeable characteristics of science-based industries: a) the appropriation of research outcomes as a property right, b) the close connection between public science research and corporate R&D and c) the financial sources that feed them.

a) In general, scientific research is conducted in distinctive institutional contexts featuring both public and private actors (Partha and David 1994). Due to the fact that scientific research is often considered a public good, private firms have a tendency to avoid investment in scientific research unless the research can guarantee a direct economic profit in the short term (Nelson 1959, Partha and David 1994).[47] Therefore, setting a patent regime for economic appropriation of research is necessary to attract private actors to science-based innovation.

b) In parallel with an increasingly stringent patent regime, the division of labour between public science research and corporate R&D has become blurred. This trend was accelerated by the Bayh-Dole Act of 1980 in the US, which allowed public-funded research to be patented (Friedman 2004). This has led to an increasing overlap between public and private sector R&D. In turn, a niche business field has emerged ‘around pre-product development’ based on 'upstream patents' of scientific discoveries (Eisenberg and Nelson 2002).[48]

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literature review. The KoPI is now viewed as transitioning from a production-based sector to an innovation-generating sector; thus, the theoretical angle is closer to the generation of science-based innovation by latecomer countries than by that within the pharmaceutical sector-specific frame. Of course, it relies considerably on the pharmaceutical industry-based literature.

[47] Traditionally, large, established firms led the scientific research for innovation, dating back to the early 1920s and as exemplified by the cases of the German chemical companies (Meyer-Thurow 1982, Mowery and Nelson 1999) and the emergence of industrial giants such as Dupont, GE and RCA in the US (Smith 1990).

[48] Related to this, the concepts in *Mode 2* of producing knowledge by Gibbons et al. (1997) and *Triple Helix* by Etzkowitz and Leydesdorff (2000) are proposed to emphasise the closing relationship between the public

c) In terms of finance, venture capital is the main funding source for the earliest stages of science-based business, specifically prior to entry into the public stock market. This new type of financing has flourished in the US (Kortum and Lerner 2000). It led to the rise of the small technology-intensive companies that drove the economic growth and employment in the US in the 1980s (Gompers 1994).

However, these three characteristics of science-based industries seem to be expressed in different ways in latecomer countries. First of all, IPR acts not only as an institutional facilitator but also as a barrier to rapid technological learning and industrial upgrade. This is particularly true in cases when patents are institutionally linked with the international trade regime. For example, the experience of the Indian pharmaceutical industry shows both sides of the impact (e.g., Kale 2005, Athreye et al. 2009). Moreover, many developing countries cannot foster science-based innovation due to weak science research capability and little financial room in the public and private sectors.

2.4.1.2 Science-driven learning and innovation

In general, two types of problem searches lead to innovation in high-tech industries such as electronics and pharmaceuticals: science-based and engineering-based. Science-based innovation, in general, involves a higher degree of uncertainty than engineering-based innovation.

Science-based innovation, such as drug R&D, builds on a small number of established paths of knowledge (Pisano 2006). As noted above, an increasing number of approaches have emerged for generating new drugs, from conventional (organic) chemistry to molecular biology to genomics. However, the scientific knowledge base is still in its infancy or development stage. Hence, it is often difficult to identify and select the 'right' path of knowledge to follow in the face of scientific uncertainty (Pisano 2006).[49] Moreover, scientific knowledge is typically produced in a highly fragmented manner, spread across individual labs in universities, public research institutes and private companies (Knorr-Cetina 1999).

An engineering-based problem search, by contrast, has a relative advantage compared with a science-based one. It is based on more certain knowledge, as many engineering-related problems can be solved based on scientifically validated core operating principles

sector (mainly universities) and the private sector (i.e., industries) in generating innovation based on public scientific research.

[49] The reproducibility of research outcomes (i.e., experiments) is also highly affected by the individual scientist's routines and experiences (Knorr-Cetina 1999). In the interpretation of this argument, they are referred to as 'results that are not readily translated from one scientist to another' (Dunne and Dougherty 2006).

and dominant designs. The scientific discoveries and principles underlying engineering problems are already known and have been further 'packaged' into the dominant design (e.g., components or products).[50] Thus, there is less need for direct involvement in fundamental science research. Moreover, engineering-related problems often have comparable (benchmarking) products or criteria (Dunne and Dougherty 2006). Therefore, engineering problems are more tangible and thus easier to identify than science-related problems (*ibid.*).

For example, engineers in electronics and semiconductors are not really concerned about 'whether the basic technology is feasible' (Pisano 2006). They can assume that their products will work regardless of functioning efficiency (*ibid.*). By contrast, drug researchers are normally unable to ascertain whether they can discover materials and biological mechanisms related to what they want to research. Furthermore, they are not sure whether the materials they discover will be feasible for use in the human body until clinical trials are conducted (*ibid.*).[51] Thus, scientific researchers have to first find out, understand and further validate the basic relationships between causes and effects. Only then can they integrate these outcomes with knowledge about biological systems – which itself is still fragmented in understanding.

On the whole, science-based innovation requires researchers to take two steps: simplification for discovery through in-vitro experiments and integration for development (Pavitt 1998). The uncertainty of innovation in development time, learning cost and probability of failure becomes high.

2.4.2 The emerging biotechnology paradigm

Biotechnology is having a number of effects on traditional synthetic chemistry-based drug R&D. The discovery and preclinical development stages of R&D have benefited from biotechnological methods since the 1990s. For example, the emergence of genomics, proteomics and bioinformatics has broadened the possibility of identifying

[50] Strictly speaking, many engineering-based industries are outcomes of technological evolution from initial science-based innovation and its further 'engineered' technologies through the use of established scientific principles. Scientific research still serves as a main driver of innovation, especially at the frontier, such as in electronics. In this context, Pavitt (1991) distinguishes the two main patterns through which scientific knowledge is applied to innovation, the application of skills and training (e.g., research techniques and basic principles) and the content of the knowledge itself. Physics, as a representative case of the former type, is widely and indirectly utilised for its meta scientific principles in the various industries. Conversely, in the latter case, biological knowledge is applied directly to the development of new products. Similarly, Marsili (2001) departmentalises the science-based industries into two technological regimes: life science-based industries, such as drugs and bioengineering, and physical science-based industries such as computers, electrical, telecommunications and instruments.

[51] Besides, the scientific experiments are conducted away from the ultimate target of the research: the biological system of the human body (Dunne and Dougherty 2006). It further poses the issue of integration of research outcomes with the biological system.

potential targets. In addition, combinatorial chemistry and high-throughput screening (HTS) have facilitated the mass synthesis of all possibilities and the rapid screening of compounds in terms of whether they fit with the target (Burns 2005: 116-122).

These processes have led to the efficient identification of potential drug candidates and reduced costs and time expenditure (*ibid.*). Owing to advances in new biotechnology and relevant chemical and information technologies, drug R&D is now transitioning from the random screening era to an era of rational drug design (RDD) (Figure 2.3).

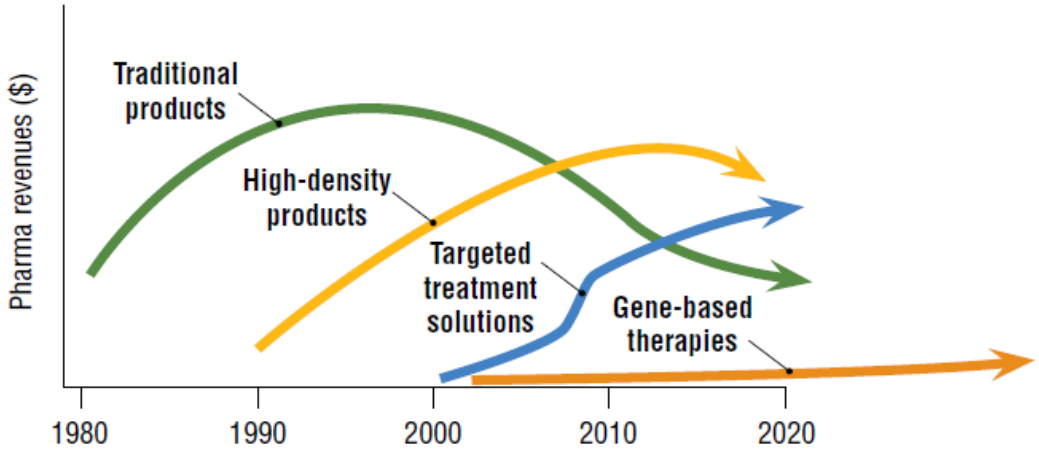


Figure 2.3: Technological evolution of drug R&D

Source: Arlington et al. (2002)

However, much about the biochemical mechanisms of diseases still remains unknown, and drug research to tackle them has had mixed results.[52] The extensive science base, the variability of approach and its immaturity of scientific knowledge of human body has led to low productivity in new drug development (Burns 2005, pp. 69–72 and Pisano 2006).

Overall, the penetration of a new biotechnological paradigm into the synthetic chemistry-based innovation pattern of drug R&D provides both opportunities and uncertainties. Biotechnologies offer various new knowledge bases and techniques to understand the human body and conduct more sophisticated drug R&D. However, the extensive knowledge base forces innovation actors to apply state-of-the-art but unstable biotechnologies to drug R&D. In brief, the present state can be described as follows: ‘on

[52] As noted, the biochemical mechanisms are approached from various science disciplines: from genetics, molecular and cell biology, and from biochemistry, bio-informatics, computational chemistry, combinatorial and protein chemistry and medicinal subjects (Pisano 2006).

the “spectrum of understanding” we sit midway between empiricism (finding out by trial and error) and engineering’ (Jon Northrup, cited in Burns 2005, p. 70).

2.4.3 Product nature as an integral product

The third feature of the knowledge dynamics stems from the nature of drugs, which have integral product architecture. Here, product architecture refers to the way the functions of a product are allocated to components or subsystems (Ulrich 1995).[53] In line with this, product architecture involves how individual research outcomes, such as materials or components, are integrated with other components/products. In general, there are two different forms of product architecture: modularity and integrality.

Modular products are developed through ‘smaller subsystems that can be designed independently yet function together as a whole’ (Baldwin and Clark 1997, p. 84). Each subsystem (or component) has its own function that is necessary for the ultimate function of the final product. They are integrated with one another as a single final product. This is based on the feasibility of the physical decomposition of a product into its various levels of subsystems or components (Henderson and Clark 1990, Brusoni and Prencipe 2001). That is, a modular product consists of high independence across subsystems and high interdependence within each subsystem (Pisano 2006). Many products related to mechanical operation belong to this category of product architecture, such as aeroplanes and computers.

In contrast, modularisation is often impossible when developing drugs because of the difficulty of physical decomposition (‘partition’) (Pisano 2006). Specifically, integral products have ‘a high degree of interdependence or interconnectedness among components or problems’ that require their ‘joint optimisation’ (*ibid*) for product function. In Pisano’s example, the modularisation of a drug into components such as an active pharmaceutical ingredient (API) and formulation parts (non-API materials) is difficult, because these two parts are organically interdependent in terms of realising product functions like efficacy and safety. Furthermore, API itself consists of a single kind of physical entity with a range of functions such as efficacy and safety.

2.4.4 Impact of the knowledge base on pharmaceutical R&D

Pharmaceutical R&D has rapidly been complicated under the three features of knowledge dynamics, particularly in the two dimensions of interactive learning: i)

[53] The concept is extensively elaborated through similar concepts such as product platforms (Meyer and Lehnerd 1997), architectural innovation (Henderson and Clark 1990), and complex product systems (Hobday 1998b).

increasing networking between heterogeneous innovation actors, and ii) simultaneous and dense interaction across R&D tasks/steps.

i) First of all, the deep reliance of biotechnological innovation on science across various disciplines has accelerated the participation of diverse public and private R&D actors in drug R&D networks. Diverse public and private innovation actors operate in heterogeneous institutional contexts and have different R&D goals, reward systems, ways of conducting research, and so on. Here, the point is the extensive R&D network for drug development leads to blurred divisions and an overlap of R&D tasks between innovation actors.[54]

- No single *pharmaceutical giant* can afford to internalise R&D for the whole system of the human body due to the limited biotechnological knowledge base. Their core competencies often reside in conventional chemistry. Thus, they need to strengthen external R&D networks to compensate for their weak knowledge base. There are various ways that pharmaceutical firms acquire external innovation sources, from a direct M&A to loose R&D collaboration and outsourcing (with DBFs and public research institutes).
- *DBFs* generally specialise in upstream biotechnology research but lack financial resources and downstream knowledge (i.e., clinical and marketing ability). They seek to develop and transfer novel drug candidates and process technologies to pharmaceutical giants.
- *Public actors,* such as universities, are rarely knowledge integrators, but are rather fragmented knowledge creators based on a high degree of scientific exploration. Their research outcomes are protected by patenting and transferred to industrial actors for further development. Unlike private R&D actors, the incentive of university research is not only patenting, but also academic reputation through publication.

ii) The functions of drugs, such as efficacy and safety, cannot be physically separated. The nature of integral products essentially imposes simultaneous, repetitive and continuous feedback across the R&D tasks and processes. The difficulty of dividing functions based on the physical decomposability of drugs can cause organisational and

[54] It is based on the literature on R&D networks in the pharmaceutical industry (e.g, Arora and Gambardella 1990, Powell et al. 1996, Galambos and Sturchio 1998, Malerba and Orsenigo 2002, Zucker et al. 2002, Quere 2003, Rothaermel and Thursby 2007). A summary of the literature is given in Appendix 1.

institutional confusion in terms of allocating R&D tasks by team, and clarifying performances.[55]

Overall, the penetration of biotechnologies into pharmaceutical R&D, with its profound science base, has necessarily drawn various public institutes and DBFs into drug R&D. Thus, interactive learning through R&D networks has become thicker and now comprises more heterogeneous innovation actors. Moreover, R&D teams need to conduct more simultaneous and dense interactions. At the same time, the 'integrality' of products makes it more difficult to effectively divide R&D tasks and teams.

2.5 New Challenge: Understanding of Science-Based Catch-Up

The final review section, first of all, poses the need for radical enhancement of an exploratory mode of learning for transition in science-based industries (Sub-section 2.5.1). It then determines the key characteristics of an exploratory mode of technological learning based on the literature review (Sub-section 2.5.2). Lastly, the limited understanding of science-based catch-up and latecomers' exploratory learning in the existing literature is summarised (Sub-section 2.5.3).

2.5.1 Challenges for science-based transition

Three unique features of knowledge in the pharmaceutical industry, combined with the general obstacles of transition, saddle latecomers with having to make radical changes in their pattern of technological learning.

First of all, the transition in the pharmaceutical industry requires a broader and deeper scientific knowledge base. Here, the point is the dual characteristics of science-based innovation, which is both fragmented and systemic. As highlighted above, when new-drug R&D is conducted, the relevant scientific knowledge is typically fragmented across various disciplines and innovation actors. At the same time, the fragmented knowledge must also be comprehensively understood in the context of a complex biological system like the human body. By contrast, in the imitation stage, which focuses on producing generic drugs, firms rarely engage in such highly explorative and integrative learning. They generally acquire scientific knowledge that has already been 'packaged' in an engineering context. A full understanding of the scientific base of the products at this point is unnecessary in reversing the product life cycle, even in drug production. Thus,

[55] In contrast, in modular products, the organisational boundaries of tasks set by each firm or team can be clearly demarcated due to the independent nature of the subsystems/components.

latecomers face significant barriers in dealing with the dual perspectives needed during the transitional phase.

Second, the integral architecture base of drugs creates a further knowledge gap between the imitation and innovation stages of development compared with what would be found in the modular products. The difficulty of physical decomposition and high interdependence between functions forces latecomers to master a complex knowledge base within a short period of time if they want to develop their own drugs.[56] In contrast, in the imitation stage, there is widely diffused information about off-patent original drugs. Thus, firms can learn through reverse engineering of synthetic processes with less need for understanding the discovery and design process of the chemical composition. However, the process-related capability will not enable latecomers to design and test novel integral products. That is, new-drug development requires a high level of exploratory learning, whereas the synthesis of off-patent drugs is based on exploitive learning.

Third, the emerging biotechnological paradigm also leads to complexity of learning in achieving science-based transition. Biotechnology can provide new opportunities for latecomer pharmaceutical firms' catch-up, just as, for example, Korean TV manufacturers exploited the emerging technological paradigm of digital technologies (see Sub-section 2.3.2).

However, being able to take advantage of these new opportunities is difficult for two reasons. One is the fact that the speed of technological advance at the frontier influences the speed of catch-up in the new technological paradigm (Mytelka 2004). This is related to how quickly the forerunners move on to new technologies (*ibid.*). If the transitional period (of technology) becomes shorter, the latecomers with a limited knowledge base will have less of a possibility to catch up due to the intense science base of the emerging technological paradigm (*ibid.*).[57] The other is associated with latecomers' direct ability to deal with institutional and organisational conditions involving new technologies (*ibid.*). Surrounding institutions must determine how they can promote the exploratory learning

[56] By contrast, modular products such as electronics and computers, have the relatively easy characteristics to realise the incremental change of the learning pattern. For example, the nature of physical decomposability underlies the successful stepwise catch-up often characterised by OEM and ODM. They initiated technological learning by supplying simple components to overseas manufacturers with limited engineering knowledge. They then incrementally expanded the supply scope of components and subsystems by improving their knowledge base. The design capability of the original product can be gradually acquired through the incremental expansion of exploration.

[57] This is based on the illustration of the increasingly difficult environment surrounding taking the catching-up opportunities in new wave technologies such as biotechnology due to the extensive scientific knowledge base, the increasing need for collaborative and interactive learning by local innovation actors and the rapidly changing technologies (Mytelka 2004).

of new technologies. In addition, it is essential that latecomer firms expand their exploratory learning to take advantage of new opportunities

On the whole, to deal with complicated knowledge dynamics, there is a need for radical enhancement of the exploratory mode of technological learning.

Table 2.1: Key characteristics of exploration in science-based industries

	Exploration	Exploitation
Basic nature of learning (Problem identification and solving)	• Distant search and learning (for future products/processes) • Ill-defined problem • High uncertainty - in cost and time • Scientific research	• Proximate search and learning (around daily production activities) • Articulated problem • Low uncertainty - in cost and time • Engineering operationalisation
Knowledge base	• Broad science subjects • Dispersed and fragmented • Immature and interconnected	• Limited science knowledge • Often packaged and manualised • Mature and engineered
Interaction	• Dense and tacit • Simultaneous • High openness and more horizontal	• Thin and codified • Sequential • Limited openness and often vertical
Competition	• Quality differentiation - novelty • Often market creation or niche focus • Patent protection base	• Cost efficiency • Established market segment • Off-patent base
Governance of leaning (Organisation/ system)	• Autonomous and loose • Active public research actors, Active science-intensive start-up • Complex and heterogeneous institutional context	• Centralised and tight • Dominated by industrial incumbents • Streamlined institutional context

Source: Own elaboration based on Gilsing and Nooteboom (2006)

2.5.2 Key characteristics of exploratory learning

The initiation and establishment of an exploratory mode of learning is the main challenge in embarking on a science-based transition. In the latecomer context, it is assumed that the smooth expansion of exploratory learning ultimately influences the speed of the transition. This subsection determines the key characteristics of exploration in science-based industries with integral products compared with those of exploitation.

The review of organisational learning (Sub-section 2.2.3), first of all, identified some basic natures of exploratory learning, which is very different from exploitive learning

(Table 2.1). In general, exploitation involves the improvement of daily production activities through proximate search and learning with low uncertainty. It is often interpreted as incremental innovation with minor modifications. In contrast, exploration is performed for creating novel products and processes by distant search and learning with high uncertainty. In particular, exploratory learning in the pharmaceutical industry involves considerable scientific research, whereas exploitive learning is mainly related to engineering operationalisation.

As discussed in Section 2.4, sector specific knowledge dynamics also influence the different patterns of interactive learning, competition and selection criteria, as well as the governance of learning mechanisms of exploratory learning from exploitive learning (Table 2.1).

2.5.3 Limited understanding of science-based catch-up

The literature on catch-up has tended to focus on modular product-based industries that successfully followed the stepwise catch-up process with incremental expansion of exploratory learning. Interestingly, none of the four Asian NIEs have yet shown significant catch-up in the science-intensive and integral product-based pharmaceutical industry. Relatedly, the process of enhancing exploratory learning in science-based industries with integral product architecture has tended to be overlooked.

The literature on science-based innovation continues to focus on the challenges of advanced countries, which have already accumulated a considerable science base and to a large extent already established the exploratory mode of technological learning. Thus, R&D collaboration and balancing exploratory and exploitive learning have become the main interests of the literature (in innovative firms). In contrast, the challenges that latecomers face in initiating and enhancing exploratory learning have been overlooked in the literature.

All in all, the existing literature has limitations for understanding the changing dynamics of technological learning, as it shifts from exploitation to exploration during the process of science-based catch-up, particularly in industries such as the pharmaceutical industry, which are based on integral product architecture. This thesis focuses on the changing dynamics of technological learning in the science-based catch-up that seems to be increasingly important to sustain industrial upgrading in the latecomer context.

2.6 Summary

This chapter has reviewed the four bodies of literature that underpin this thesis's main research problems, the formulation of research questions and the construction of its conceptual frameworks.

First, key theoretical concepts on the general innovation process in the latecomer context were reviewed. In the literature on micro-level technological capability, the transition of latecomers was discussed in terms of a qualitative reinforcement of the exploratory mode of technological learning to overcome the imitation stage. The macro-level institutional setting was then discussed by presenting a restructuring of two innovation systems (NIS and SIS) to promote innovation actors' exploratory learning.

The review of the empirical literature first explored the common features of rapid catch-up, discussing the stepwise catch-up model of the Asian NIEs. This model is driven by enhancing absorptive capacity and acquiring export markets. It then showed that recent empirical studies of the transition clearly confirm the need for changes in organisational and institutional mechanisms from imitative learning to innovation generation. The transition of the KoPI can be interpreted within this frame.

Moreover, the review of the literature on science-based innovation showed that there is a bigger gap in technological learning between the imitation and innovation stages in the pharmaceutical industry, with its integral product architecture, than in the major catch-up industries that make modular products.

The review finally determined the key characteristics of exploratory and exploitive learning in the science-based pharmaceutical industry. It also pointed out that existing studies have only a limited understanding of the dynamics of science-based catch-up. On this basis, the next chapter establishes the research problems, research questions and a framework.

Chapter 3: Research Questions, Frameworks and Methodology

3.1 Introduction

This chapter consists of three parts. First, it identifies the main research issues and formulates the research questions (Section 3.2). Conceptual and analytical frameworks are then constructed (Sections 3.3 and 3.4). The research methodology is then presented, clarifying the overall research strategy and the structure of the data collected (Section 3.5); this is then followed by a summary (Section 3.6).

3.2 Research Issues and Research Questions

This section explains the thesis's research objective and its corresponding research questions. It is based on the identification of the main research issues, which are not known by the preliminary data on the transition of the KoPI (Sub-section 3.2.1). The research objective and ensuing research questions are then laid out (Sub-section 3.2.2).

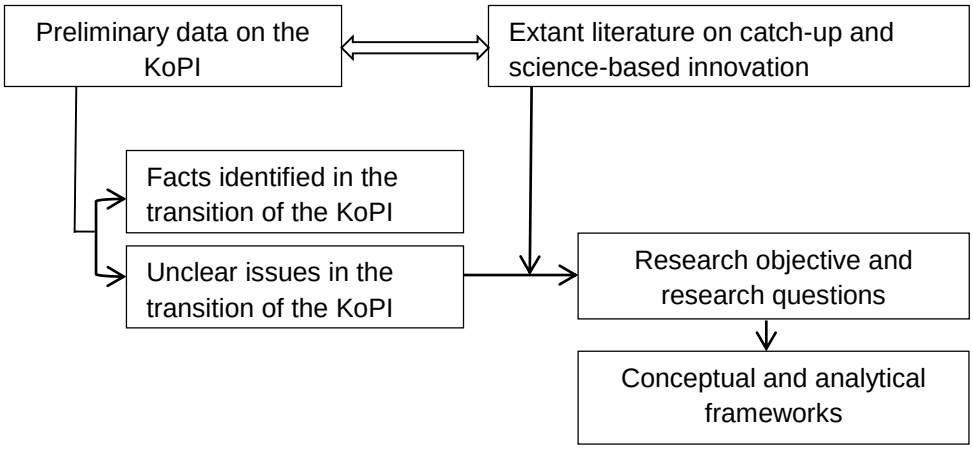


Figure 3.1: Formulation of research questions and frameworks

3.2.1 Research issues

The literature review first recalled that strengthening organisations' ability to conduct more distant search and learning helps them accumulate innovative capability. This type of learning was conceptualised as exploratory learning, and contrasted with exploitive learning.

The review then identified a series of challenges faced by latecomers during their transitional phase. For example, latecomer firms are exposed to more direct competition

with forerunners in more novel product markets. This requires more internal technological and strategic capabilities. Similarly, latecomer countries face institutional challenges in moving from innovation systems based on knowledge utilisation to systems based on knowledge generation.

The challenges of transition are more difficult in the pharmaceutical industry because of its unique knowledge dynamics. Three features of the sectoral knowledge base widen the gap between the imitation and innovation stages: an extensive science base, integral product architecture and the diffusion of new biotechnologies.

In line with this, the review argued that both quantitative and qualitative reinforcement of the exploratory mode of technological learning become necessary to overcome the heightened barriers to transition in the pharmaceutical industry.[58]

Meanwhile, preliminary data on the KoPI roughly estimated the rate of transition, which can be identified through clarifying the starting point of new-drug R&D and the present outcome of the new drugs developed. The following statements can be made about the transition of the KoPI.

a-1) The transition began soon after the introduction of the product patent system in 1987 and was deeply affected by the NHI reform of 2000. Emerging biotechnology served as the other critical force influencing the transition since the early 1990s. These institutional and technological changes were the *force majeure* that directed the transition toward the development of innovative drugs and away from the purely imitative production of generic drugs.

a-2) As the intermediate outcome of the transition, by 2014 about 25 new drugs had been developed domestically (i.e., approved by the KFDA), and two had acquired an NDA from the US FDA. These data signify the present status of the industry and the rate of the transition to date, particularly in terms of technological catch-up.

a-3) The preliminary data also confirmed that firms' new-drug R&D has gone along with the reform of S&T policies. This includes a rapid scaling-up in national R&D investment, an increasing drug R&D support by some ministries and the introduction of new incentive and evaluation systems. The aim of the policy changes was to make the country an innovator rather than a proficient imitator.

[58] See Hopkins et al. (2007) for more details of the sector-specific difficulties.

a-4) On the whole, the firms' 25 new drugs and policy reforms supporting innovation generation firmly suggest that exploratory learning, at first glance, has been enhanced.

a-5) However, most of the market profit of the KoPI has continued to be sourced from the imitative production of generic drugs, even after the 25-year transition effort.[59]

These facts highlight a key issue about the process and speed of the transition: has the present status (rate) of transition been reached in a relatively smooth manner, or has it been interrupted? This question directs us to examine the influence of institutional and organisational factors on the process of enhancing exploratory learning and the rate of transition. As noted, institutional and organisational mechanisms shape the pattern of technological learning and influence the speed of catch-up.[60]

Overall, this research seeks to understand firm- and institutional-level factors that might have affected the heightening of exploratory learning and therein the achievement of the latecomers' science-based transition.

3.2.2 Research objective and questions

In line with this, the research objective is as follows:

Research objective:
To understand the factors that determine the enhancement of the exploratory mode of learning, and therein ultimately influence the rate of a science-based transition.

[59] Only three new drugs are estimated to have exceeded the minimum level of the domestic market expectation. Like the blockbuster in a global context (i.e. USD$1 billion per year), ten billion won (KRW, about $0.1 billion) of revenue per annum has been the practical criterion of market success in the domestic market.

[60] There seems to be another approach: focusing on the singular perspective of the knowledge dynamics in science-based innovation. One can simply ascertain that most latecomer countries in the short- and mid-term cannot resolve the sector-specific knowledge dynamics, i.e. the weak scientific knowledge base and the wide gap of market segments between generic drugs and original drugs that are strictly divided by the global patent system. Relevant to this are comments from a few scholars: 'Survival of the KoPI itself under the changing institutional change and Big Pharma leadership can be seen as a success' (comment by Steinmueller); 'No latecomer countries have succeeded in taking the stable position of new drug developers. Even among the advanced countries, only a few countries such as the U.S., the U.K. and Germany [and France] have kept the position in the pharmaceutical industry' (comment by Orsenigo). However, unlike the pharmaceutical industries in other latecomer countries, the preliminary data showed that the KoPI has challenged the development of its own new drugs with the overall reform of S&T policies, including the national support of biotechnology. It leads the research to focus on the institutional and organisational perspective rather than the intrinsic knowledge dynamics themselves.

Research questions are formulated to narrow down the focus of the research objective and further provide a rationale for building a conceptual framework.[61] In this thesis, the two dimensions of the research issue identified above – institutions and organisations – shape the scope of the research focus.

The first research question deals with how latecomer countries attempt to institutionally facilitate innovation actors' exploratory learning. Accordingly, the first sub-question seeks to uncover the influence of the reformed S&T policies on strengthening exploratory learning in R&D organisations. It particularly concerns whether the basic characteristics of exploration identified previously, such as a highly distant search and a long period of learning, are promoted under the new S&T policies. The second sub-question seeks to understand the influence of the policy reforms on encouraging interactive learning across R&D organisations, which is another key feature of exploratory learning. Specifically, it focuses on the interaction between the exploration practices of private and public innovation actors, an institutional arrangement that has become necessary in the current science-based pharmaceutical industry.

The second research question handles how effectively latecomer firms actualise the key characteristics of exploration in their new-drug R&D projects. As seen, latecomers' new-drug R&D can be interpreted through two dimensions on exploration practices. One is related to the dimension of technological learning practice for new-drug R&D. The other involves the organisational dimension surrounding the technological learning practice.

Research questions:

RQ 1: How have S&T policy rearrangements affected innovation actors' enhancement of the exploratory mode of technological learning?

RQ 1.1) How have the reformed S&T policies influenced exploration practices in R&D organisations?

RQ 1.2) How have the reformed S&T policies influenced interactive learning between public and private innovation actors?

RQ 2: How have latecomer firms strengthened the exploratory mode of technological learning for new-drug R&D?

[61] The research questions are set up using the following rationale. First, the research questions help the research focus on certain aspects of the broadly identified research problem (Van de Ven 2007). Moreover, the research questions lead to the building of a conceptual framework, and guide the collection and analysis of the data (Miles and Huberman 1994). Overall, the research questions provide the research with a more substantial guide to address the research objective and to create the research design.

RQ 2.1) How has the exploratory mode of technological learning been reinforced in new-drug R&D practices?

RQ 2.2) How have firms' organisational mechanisms been reconfigured to deal with exploration-driven new-drug R&D activities?

3.3 Theoretical Framework

This section presents a conceptual framework for both institution- and firm-level dynamics that promote exploratory learning. In the institutional dimension, the policy rearrangement involved in new-drug R&D and its influence on learning practices is conceptualised using an SIS. The firm-level dynamics focus on technological learning and corresponding organisational mechanisms. They are framed by organisational learning aimed at exploration.

An underlying viewpoint of the sectoral transition is first outlined (Sub-section 3.3.1). Subsequent sections then expound on the theoretical focal points to trace the institutional and organisational perspectives of enhancing the new form of learning (Sub-sections 3.3.2 and 3.3.3).

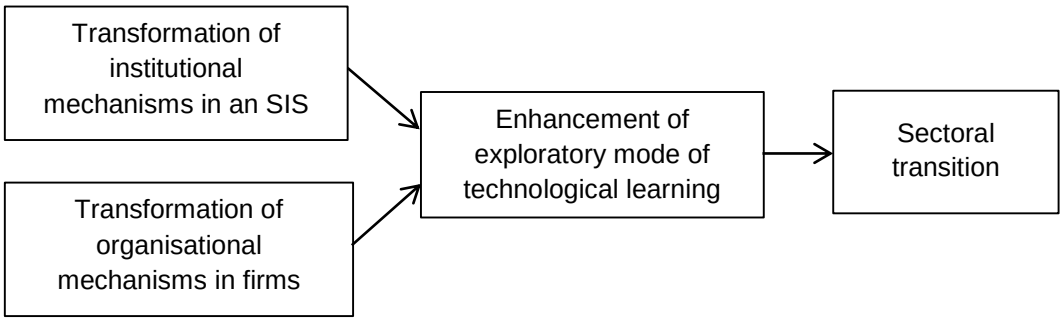


Figure 3.2: The transformative view of the sectoral transition

Source: Own elaboration

3.3.1 Sectoral transition as transformational process

The conceptual framework is built on the view that latecomers' transition involves the transformation of institutional and organisational mechanisms. It is based on the assumption that technological learning is promoted or stumbled upon by certain institutional and organisational mechanisms. In particular, in the transitional phase, the institutional and organisational mechanisms are engaged with the unlearning of the previous, imitation-oriented learning pattern and the strengthening of the innovation-oriented learning pattern. The previous chapter argued that latecomers' innovation-

oriented learning in the pharmaceutical industry is driven by the enhancement of the exploratory mode of learning. In line with this, the rate of transition is assumed to be influenced by the effectiveness of institutional and organisational transformation to promote the key characteristics and conditions of exploratory learning (Figure 3.2).[62]

The following two sub-sections present the organisational and institutional elements that might have influenced the intensification of innovation actors' exploratory learning (Table 3.1). These elements are identified using the concepts of SISs (Sub-section 3.3.2) and firms' organisational learning (Sub-section 3.3.3).

Table 3.1: Conceptual framework of a latecomer sectoral transition

Dimension		Elements of transformational process
Innovation systems	Governance of S&T policies	a) Investment b) Incentive and evaluation c) Industrialisation of exploratory learning d) Alignment of relevant policies
	Behaviours of innovation actors	(Under governance) e) Exploration practices within an organisation f) Mutual interaction in exploration practices across actors
Firms' organisational learning	Technological development	g) R&D process h) R&D strategy
	Organisational mechanisms	i) Organisational structure j) Top management k) Mind-set of individual actors

Source: Own elaboration

3.3.2 System-level transformational process

The concept of an SIS underpins the institutional-level transformation. An SIS consists of various innovation actors and institutions that characterise the relationship between innovation actors in relation to knowledge creation, production and competition. As stated, in the imitation stage, an SIS is initially created for the efficient production of imitative products such as generic drugs. Innovation actors and relevant policies focus on exploiting externally existing technologies for economical production. In this stage,

[62] Of course, this does not imply the rejection of the nature of technological, organisational and institutional continuity, often expressed as cumulativeness, routine or path-dependency in industrial evolution. Rather, the transformative view is the conceptual frame for recognising the systemic and behavioural changes in the transitional phase.

knowledge generation is largely confined to improving process technologies for more efficient use of existing technologies.

The knowledge-generating activities in an SIS are expanded when latecomers try to innovate in the transitional phase. This role of an SIS can be identified in the changing institutional mechanisms, such as the rearrangement of S&T policies (Sub-section 3.3.2.1) and their influence on innovation actors' exploratory learning (Sub-section 3.3.2.2). That is, an SIS in the transitional phase is understood in terms of how the SIS and relevant S&T policies evolve toward promoting exploratory learning to cope with the sector's complex knowledge dynamics.

3.3.2.1 S&T policies – investment, incentive, industrialisation and alignment

Three policy categories cover the major aspects of innovation activities, such as resource input, its operation and output generation: a) investment policies for innovation actors, b) incentive and evaluation policies for innovation activities and c) industrialisation policies for exploratory learning. These are drawn from the literature on the catch-up of Asian NIEs (Chapter 2, Sub-section 2.3.2).

a) Investment policies for innovation actors

The first pressing policy is the structural establishment of new innovation actors that can perform advanced exploratory learning, and the restructuring of established actors that focus on technological assimilation and exploitation. The SIS of the pharmaceutical industry requires the participation of various innovation actors, including public researchers such as GRIs and universities, and private actors such as biotechnology start-ups and incumbent pharmaceutical companies.[63]

In the latecomer context, the rapid fostering of such innovation actors is a significant challenge. In particular, given the industry's weak research and financial capabilities, national R&D investment is a critical means to foster public research actors and research-based start-ups. This can be done by building science-related infrastructure such as science parks, and by providing national support to universities to heighten research capabilities. Such national efforts promote an exploratory mode of learning. To use a more specific example, the take-off of commercial biotechnology in the US in the 1980s was based on government investment in public innovation actors in molecular biology in the 1960s and 1970s (Collins 2004, p. 88 and p. 126).

[63] In addition, competent regulatory entities that can monitor and guide science-based innovation activities become necessary.

b) Incentive and evaluation policies for innovation activities

Another key point relates to the effective operation of national R&D investment to promote innovation activities. This involves understanding how incentive and evaluation systems encourage innovation actors to conform with the key features of exploratory learning, which is the key mode of learning in pharmaceutical R&D. For example, there must be incentives to promote innovation actors' engagement with ill-defined scientific problems, as well as long-term and highly uncertain research related to drug discovery. Collaborative research across diverse innovation actors must also be incentivised.

In the successful catch-up industries in Asian NIEs, rapid technological assimilation and its translation into profit were driven by providing various incentives along the path from technological learning to market creation. This is often referred to as a 'carrot and stick' policy.

In the emerging science-based industries, the conventional focus on competitiveness of industrial technologies is being replaced by concerns about research capability. For instance, national focus on encouraging scientific publications reflects a policy trend to promote exploratory learning in Asian NIEs. However, it should be noted that the scientific outcomes need another process for commercialisation, unlike the previously mentioned catch-up industries.

c) Industrialisation of exploratory learning

Promoting the commercial translation of research into profit becomes another policy challenge for the latecomer countries. S&T policies can promote the coherent interconnection of heterogeneous and dispersed exploration practices, ranging from public upstream science to industrial R&D.[64]

Conceptualising two contrasting directions of exploration practices seems to be useful to trace the interconnection of diverse exploratory learning: research-oriented exploration and business-oriented exploration. Research-oriented exploration is mainly conducted for knowledge generation by public actors such as universities and GRIs; it is less goal-oriented, less profit-seeking and highly fragmented across academic subjects and laboratories. In contrast, firms' business-oriented exploration has a clear goal of developing commercial products. For example, while universities and firms may both

[64] This point is also based on a few popular concepts such as Mode 2 of producing knowledge (Gibbons et al. 1997) and Triple Helix (Etzkowitz and Leydesdorff 2000), which deal with the relationship between the public sector (mainly universities) and the private sector (i.e. industries) in generating innovation based on public scientific research.

engage in exploratory learning, universities tend to prioritise academic publications, while firms prioritise patenting.

In the imitation stage, policies for supporting the industrialisation and commercialisation of technological learning worked relatively well. The close relationship between technological learning through reverse engineering and its direct applicability to industrial practice underlies the effective support of commercialisation. More straightforwardly, the scope and direction of technological learning was determined based on industrial utility. That is, technology policy can be regarded as the sub-policy dimension of high-level industrial policy. Science policy merely influenced the industrialisation of technological learning in the imitation stage.

In contrast, in the transitional phase, the increasingly long R&D cycle from upstream scientific research to downstream development came to cover both research- and business-oriented exploration. As a result, the high interdependence between public research and corporate development raises the need for a comprehensive industrialisation policy that can connect their dispersed exploration practices. Here, the conceptual focus involves the administrative roles of concerned ministries in dealing with industrialisation, that is, the downstream development of upstream science research, in that multiple ministries are the real designers and conductors of relevant policies.

d) Alignment of S&T policies

The concept of 'network alignment/misalignment' (von Tunzelmann 2010) provides the basis for understanding the complicated dynamics of S&T policy and its influence on exploratory learning.[65] 'Alignment' is defined as the orientation of various functions, resources and spaces to produce 'mutually compatible outcomes'. Conversely, network misalignment indicates the mismatch of outcomes produced by elements of the network, despite the fact that they have the overall same development goal (von Tunzelmann 2010, von Tunzelmann et al. 2010).[66] Von Tunzelmann et al. argue that the lack of dynamic interactivity between elements is one of the main causes of misalignment.

[65] In brief, the original concept of network alignment was concerned with the highly complicated issue of the economic transition of central and eastern European countries (CEECs) from a state-driven to a market-driven production system. The transition involves the reorientation of a production system with various economic elements such as actors, resources and functions including finance, management, technology and production skills. Domestic resources and functions that were once organised under state-driven hierarchical national production systems were reorganised under market-based systems led by multinational corporations (MNCs) (ibid.). Therefore, in the transitional process, these economies faced a series of institutional and industrial complications stemming from the heterogeneous global, national and local networks with different production contexts (ibid.). The alignment of global, national and local networks is argued to be critical for sustaining transition (ibid).

[66] Three types of network failures are suggested, arguing that the misalignment originated from a kind of network failure: (a) the absence of the network (i.e. the innovation system in this study) required for

In this thesis, alignment is an important aspect of the industrialisation policy on scientific research identified above. Specifically, it has to do with the ability of policy alignment to connect dispersed exploratory learning between public research and industrial R&D.[67] The extremely long drug R&D process cannot be deployed without institutional coordination due to the different directions of business- and research-oriented exploration and the increasing involvement of plural ministries in the industry. Therefore, various S&T policies must be coherently aligned so that heterogeneous innovation actors can perform mutually compatible exploratory learning, thereby producing beneficial learning outcomes through dynamic networking in an SIS.

3.3.2.2 Behavioural pattern of exploration practices

The other dimension to understand the knowledge-generating function of an SIS is the real influence of changing policy dynamics on innovation actors' exploration practices. The influence on the micro-level learning process is in line with the two sub-research questions. One is the intra-organisational response to the policy reform when innovation actors conduct exploration practices (E in Table 3.1). The other is the response in inter-organisational R&D collaboration, in particular between public and industrial actors (F in Table 3.1).

3.3.3 Firm-level transformational process

This sub-section determines the conceptual focus of latecomer firms' organisational mechanisms of technological learning by drawing on ideas about firms' exploratory learning. There are two conceptually useful dimensions of organisational transformation. One deals with latecomers' technological development practices in proceeding with drug R&D (Sub-section 3.3.3.1). The other considers the organisational mechanisms that correspond to technological development practices (Sub-section 3.3.3.2).

development; (b) the presence of the network with no direction toward the development goals; (c) the presence of the network toward the development goal, but 'the outcomes from its components are mutually inconsistent (misaligned)'.

[67] It is particularly related to the mix of two heterogeneous institutional spheres and its potential risk to undermine the key characteristics of exploration. The operational mechanisms of the science system are strongly affected by the business system and therefore affected by the more profit-creating rules; they will lose the diversity of scientific research and thus ultimately lose the innovation sources (Kaufmann and Tödtling 2001).

3.3.3.1 Technological development practices

The R&D process and R&D strategy are the two conceptual constituents of technological development practices. The R&D process for a new drug is the actualisation process of an exploratory mode of technological learning (g). R&D strategy involves the commercial effectiveness of latecomers' technological development practices in the changed competition environment (h).

g) *Exploration practices in the R&D process*

If they attempt to develop new drugs, latecomer firms essentially pass through a transformation from exploitation-centred to exploration-oriented technological learning. New-drug R&D requires a change in the process logic and habits of technological learning, in comparison with the development of generic drugs.

Specifically, the production of generic drugs is mainly based on technological exploitation, although the imitative production itself can be regarded as an outcome of exploration in the very early stages of learning for latecomers. The development of generic drugs hardly needs the discovery and validation process of drug candidates – the dominant methods and detailed goals of development are already known. Interactive learning thus takes place in a relatively codified manner and under the well-defined division of R&D tasks.

In contrast, the original development of new drugs needs a high degree of scientific discovery and validation. Scientific research is highly explorative and takes a long time. Simultaneous and dense interaction between R&D actors and across R&D tasks is needed for joint validation and optimisation. In other words, the characteristics of exploratory learning are notably expressed in the new-drug R&D process.

Latecomers' new-drug R&D practices can be understood as adapting to the key characteristics and conditions of exploration, as well as unlearning the ingrained learning mode of exploitation.

h) *R&D strategy in the transitional phase*

As noted, firms' exploratory learning is ultimately directed at creating economic profit. In this regard, business-oriented exploration needs strategic consideration to cope with the changing competitive environment in the transitional phase. That is, new drugs to be developed through exploratory learning should be sellable in competition with drugs launched by Big Pharma.

To begin with, in broad terms, the stepwise catch-up model seems to be strategically effective in the overall catch-up path of the KoPI. The KoPI has initiated catch-up through

following the reverse PLC and then entering new-drug R&D stages like other successful catch-up industries have done.

However, entry into the transitional phase faces latecomers with a more complex catch-up environment (Chapter 2, Sub-section 2.4). First, they face direct competition with Big Pharma. Second, they are exposed to broader technological and institutional contexts, as their R&D expands to both upstream science and downstream clinical development. For example, the inclusion of new drugs in latecomers' product portfolios forces them to deal with various institutional contexts, such as drug pricing and approval-related institutions. Third, they must grapple with the emerging biotechnology paradigm with unarticulated markets, which provides both opportunities and threats for catch-up.

Therefore, identification of the strategic response of the changing technological, market and institutional environment is crucial to understanding latecomers' exploratory learning. Based on the literature review on latecomer firms' transitions (Chapter 2, Sub-section 2.3.1), the changes in paths, focal area and commercialisation of new-drug R&D are considered to analyse latecomers' strategic strengths and weaknesses.

3.3.3.2 Organisational mechanisms

The other area of focus lies in organisational mechanisms of technological exploration. This issue includes organisational and managerial adaptation to the key characteristics of exploration and casting off the organisational routine of exploitive learning (e.g. Levinthal and March 1993, Benner and Tushman 2003, Raisch and Birkinshaw 2008). In particular, organisational structure is crucial because the design and operation of organisational structures for R&D can influence latecomer firms' organisational capability in dealing with the key mode of technological learning for developing innovative drugs. Additionally, individual-level issues, such as the role of senior management and organisational code, are underlying factors of organisational transformation.

i) Organisational structure

A company can balance the two seemingly incompatible types of learning by setting up 'dual organisational structures' that perform exploitation and exploration (Duncan 1976). Through operating a dual organisational structure, firms can guarantee their present (through exploitation) and future (through exploration) survival (Levinthal and March 1993). Ambidextrous organisations are composed of loosely coupled exploitive and exploratory sub-units; each sub-unit should be internally consistent in terms of culture, goals and individuals (Benner and Tushman 2003).

More specifically, in order to guarantee autonomous exploratory learning, firms may operate smaller sub-organisations devoted to exploration while concurrently running larger sub-organisations committed to exploitation (Tushman et al. 1997). Explorative sub-units are ‘smaller and decentralised with loose cultures and processes’, whereas exploitive sub-units are ‘larger and more centralised, with tight cultures and processes’ (*ibid.*). This physical separation of sub-units has been one of the prominent theoretical solutions for building ambidextrous organisations.

However, in the context of latecomer firms, the most important thing is not balancing exploration and exploitation, but on enhancing exploration. Therefore, the organisational structure of R&D must be reconfigured away from technological exploitation. In this context, two characteristics of exploration are particularly related to organisational structure. One is the influence of the structure of R&D organisations on the interactive learning between R&D teams. A multidisciplinary knowledge base and integral product nature impose the need for active and simultaneous interaction (Chapter 2, Sub-section 2.4). The other is associated with the organisational design for sustaining exploratory learning. It considers latecomer firms’ high vulnerability if they continue exploratory learning.

j) The role of senior management

Top management, often company owners in the case of the KoPI, also plays an important role in sustaining the vulnerable learning mode of exploration. Striking a balance between the two modes of learning requires not only the autonomous operation of exploratory sub-organisations, but also the contextual guidance, coordination and integration of the two learning patterns (e.g., Andriopoulos et al. 2009, Raisch et al. 2009). For example, coordination is critical in resolving tensions and conflicts that arise during resource allocation to each sub-unit. Guiding whether R&D organisations focus on more incremental (exploitive) or radical (explorative) innovation activities is also vital. These tasks are the responsibility of senior management teams (Tushman, Anderson et al. 1997, Benner and Tushman 2003, Jansen et al. 2008).

Therefore, for latecomer firms, the theoretical focus here examines whether top management promotes or interrupts the initiation and strengthening of exploratory learning. As noted, exploratory learning is particularly vulnerable in a latecomer firm because of a lack of short-term profitability and need for long-running R&D; such firms are financially weak and small in size. Because of this, initiative taken by top management is likely to be a critical factor.

k) Organisational code

March (1991) identifies the relationship between individual behavioural patterns and organisational code as an influential factor in conducting exploration. The exploitation-oriented organisational inertia of latecomer firms may inhibit the emergence of exploration-oriented learning by individual researchers when the company starts new-drug R&D. A generalised solution is the proper turnover of individuals to sustain exploratory learning (March 1991).

3.4 Analytical Framework

This section describes the thesis's analytical framework. This framework provides the conceptual focus for the empirical analysis. First, the system-level analytical framework (Sub-section 3.4.1) is presented, followed by the firm-level analytical framework (Sub-section 3.4.2).

3.4.1 System-level analytical framework and its elements

In this conceptual framework, institutional transformation is conceived as the rearrangement of S&T policies and their influence on innovation actors' exploratory learning in the context of an SIS. An evolving SIS in the transitional phase is seen as the functional expansion of the system into active knowledge generation by encouraging innovation actors' exploratory learning. Three policy categories are examined to understand institutional transformation: policies for R&D investment, incentive regimes and industrialisation. Policy alignment was also considered for dynamic exploratory learning.

In line with this, the analysis focuses on addressing the rearrangement of S&T policies and their influence on innovation actors' exploration practices (Figure 3.3). Two analytical dimensions are outlined. Dimension A provides the overall institutional and market background of initiating new-drug R&D. Dimension B is the foreground of the analysis, in which substantial S&T policies are operated and exploration practices take place.

(A) Market selection environment and landscape of S&T policies

As stated, the transition of the KoPI was initiated and accelerated by a series of external institutional and subsequent market changes at two points in time, (i) after the introduction of the product patent system in 1987 and (ii) after the NHI reform in 2000 (A in Figure 3.3). At the same time, the macro-level national goal for S&T investment has changed during the transition from imitation- to innovation-based economic development.

This includes greater national attention to emerging biotechnology and a range of reforms of substantial S&T policies.

Thus, to begin with, this research addresses external institutional pressures, changed market structure and the changed landscape of S&T policies (Chapter 4).

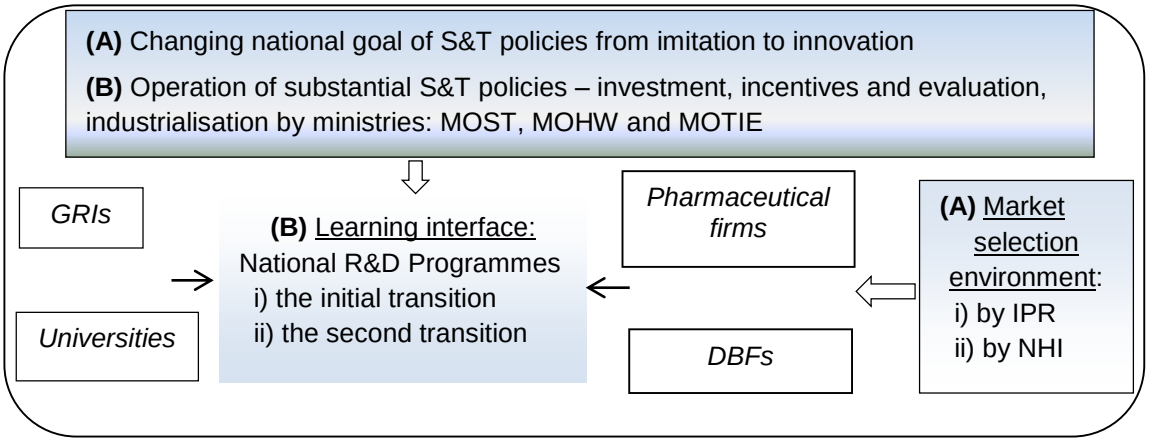


Figure 3.3: System-level analytical framework of the transition of the KoPI

Source: Own elaboration based on Vanichseni's industrial innovation system

(B) Effect of S&T policy changes on NDRPs

The impact of the revised S&T policies on exploration practices can be addressed by looking at the changes in operational mechanisms of NRDPs. This analytical frame is based on the conceptual focus on whether both research-oriented and business-oriented exploratory learning have been well promoted and interlinked under the changing S&T policies.

First of all, the operational mechanisms of the three policy categories identified above – R&D investment, an incentive regime including both incentive and evaluation of national R&D projects, and the industrialisation policies of the three leading ministries in new-drug R&D support – are analysed. The responses of private and public innovation actors (including universities, GRIs, DBFs and pharmaceutical firms) to the operational pattern of the new S&T policies are examined. In doing so, the pattern of innovation actors' enhancement of exploratory learning under the institutional changes is empirically examined.

NRDPs are the main object of the analysis; they represent a practical space where a conceptual SIS and its expansion of function to knowledge generation can be captured. There are two key features of NRDPs. First, they can be seen as the institutional interface between S&T policies and innovation actors. The operating mechanisms of NRDPs are

shaped by the three main S&T policies: national R&D funding, industrialisation policy by the three ministries, and incentive and evaluation policies for R&D funds. Thus, innovation actors participating in the NRDPs are naturally influenced by S&T policies. Second, NRDPs also serve as a collective and interactive learning space between diverse participants from both the public and private sectors.

The analysis of the NRDPs is mainly conducted based on data from the three large-scale, long-term projects under the 21c Frontier Programme: functional proteomics, intelligent microsystems, and microbial genomics and applications. These projects were all conducted over the last decade. However, the analysis takes a general approach to identify the policy impact and different responses by innovation actors, not an in-depth historical analysis of each project. This is because no project covers all the steps of new-drug R&D from upstream target identification to the development stage.

3.4.2 Firm-level analytical framework

The conceptual framework of the firm-level transformational process emphasised that the organisational adoption of the key characteristics of exploratory learning is critical for latecomers' successful new-drug development.

The analytical framework is composed by applying the concept of exploration and exploitation to the proprietary-product-process grid model developed by Forbes and Wield (e.g., Forbes and Wield 2002) (Figure 3.4). This original model can be thought of as the applied version of the latecomers' reverse PLC in the patent-based pharmaceutical industry (see Figure 2.2).

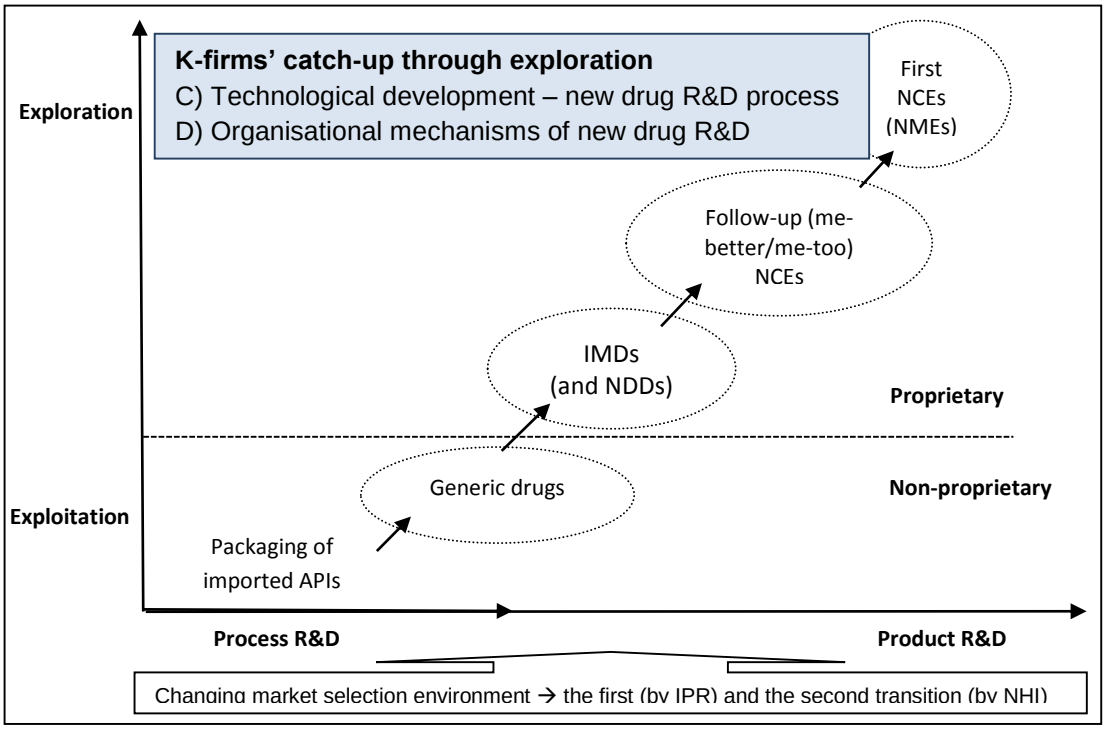
The analytical framework draws on the model with minor modifications for the empirical observation of the increasing degree of the exploratory mode of technological learning in the KoPI's expansion to new-drug R&D. The x-axis is formed by process R&D and product R&D, following the original model. The y-axis represents increasing exploratory learning as latecomer firms' R&D moves up to develop more novel products.

Taking together the two axes, the pharmaceutical drugs can be classified into four groups (Figure 3.4). The first group is generic drugs, including the production of existing APIs with the lowest level of exploration effort. Because off-patent original drugs are free for copying, latecomers can master production technologies of these drugs through reverse engineering. Thus, in practice, this product group can be thought of as the exploitation-driven product group. Most developing countries remain in this development stage.

The second group consists of incrementally modified drugs (IMDs) with minor levels of modification of the original drugs. The drugs are developed by changing some peripheral parts of the original drug molecule or improving the drug delivery system, making it easier to absorb or digest. IMDs have partial patent rights related to the aspect of the drug that was changed. A certain level of exploratory technological learning is necessary to develop IMDs.

The third product category is follow-up NCEs. These accompany a high level of exploratory learning and are fully protected for 20 years by product patents. Although this kind of drug is developed based on the same chemical platform as earlier NCEs, the full cycle of new-drug R&D, including drug discovery and optimisation and clinical trials, is conducted. A very low number of developing countries reach such degrees of exploration.

The fourth category is entirely novel NCEs that are developed through the highest level of exploratory learning, through a process of establishing an unknown chemical platform, that is, a lead compound. The drug research starts from zero, which means there are no benchmarking drugs with the same biochemical mechanism; this type of NCE thus needs a very profound scientific base. A few developed countries are mainly involved in this technological stage.



* New Drug Delivery System (NDDS), New Molecular Entity (NME)

Figure 3.4: Firm-level analytical framework of the transition of the KoPI

Source: Author's modification of proprietary-product-process grid model (Forbes and Wield 2002)

Based on this, the exploration practices (new-drug R&D) of nine domestic firms are analysed, first from the perspective of technological development in the transitional phase (C in Figure 3.4), then examining how well the firms' internal organisational/managerial mechanisms fit with the characteristics of exploration (D in Figure 3.4).

(C) Technological development based on exploration

Technological learning based on exploration is analysed in two transitional rounds: (i) the first round completed between 1987 and the early 2000s, after the introduction of the product patent system, and (ii) the on-going second round since the 2000s, in the context of NHI reform. Prior to 1987, Korean pharmaceutical firms focused almost singularly on the production of generic drugs and existing APIs. Exploitive learning was the main form of technological learning. This was despite the fact that there had been continuous advancement of the technological capability to master the synthetic technologies of known APIs in the 1970s and 1980s, starting from the point of simple packaging and formulation of imported APIs in the 1960s. The exploratory mode of technological learning was, in practice, initiated after 1987 when pharmaceutical firms first attempted to develop their own new drugs after the introduction of the product patent system.

The growing process of exploration is addressed by identifying the similarities and differences of new-drug R&D patterns between the two rounds. The analysis focuses on the procedural barriers to new-drug R&D practices and how firms overcame these barriers, as well as the path, focal area, and commercialisation of new-drug R&D.

(D) Organisational mechanisms for exploration

The change in the overall organisational structure of R&D centres is examined in terms of how well the organisational structure fits with the key characteristics of exploration. Moreover, the role of top management and the influence of organisational routine on latecomers' exploitation and exploration are addressed.

3.5 Methodology

The last section presents the overall research strategy (Sub-section 3.5.1), methods of data collection to operationalise the research design (Sub-section 3.5.2), and an explanation of how the data will be analysed and interpreted (Sub-section 3.5.3).

3.5.1 Research strategy and design

The research aims to investigate the factors that might have influenced the reinforcement of the key mode of technological learning for transition and, hence, the present status of the KoPI's transition. The study takes an interpretive approach based on qualitative data analysis, rather than a positivist approach for statistically inferring the causal relationship of events. It is a process study that deals with 'how things change and develop over time' (Van de Ven 2007, p. 194). Spender (1996, p. 72) clarifies these two different approaches: 'The object of positivist research is the development of a coherent abstract representation of the world out there, the presumed and independent seamless but knowledge reality in which we are embedded. The focus of the interpretive research is on the ways in which attach meaning to our experience'.

As this research pertains to the interpretation of latecomers' historical experiences of science-based catch-up, and seeks to analyse the managerial/policy side of the innovation process, it takes an interpretive approach using qualitative case studies. This helps determine how certain institutional and organisational factors influence the enhancement of exploratory learning and the present status of the transition. Three key aspects of the overall research strategy that were already applied above are encapsulated here.

3.5.1.1 Rationale of the conceptual framework

The conceptual and analytical frameworks were designed by drawing on previous literature and applying a transformative view of institutional and organisational mechanisms. The frameworks treat the sectoral transition as a function of the system-level and firm-level changes made to promote exploratory modes of technological learning.

The decision to use this transformational view was made because of the limited applicability of the typical conceptual approach to an investigation of the transition of a latecomer science-based industry. An incremental view of technological capability building can explain the success of catch-up in technology- and engineering-based industries such as electronics. However, the review showed that science-based transition, particularly in integral architecture-based industries, needs a more radical view of change to interpret the discontinuity of institutional and organisational mechanisms between the imitation and the innovation stages.

3.5.1.2 Embedded single case study

This thesis makes use of two embedded units of analysis: innovation systems (at a macro-level) and firms' learning dimensions (at a micro-level).

Innovation systems are used to analyse the influence of the S&T policy rearrangement on the promotion of exploratory learning. While the SIS of the KoPI is treated as a formal unit of analysis, the practical scope and degree of the analysis of the SIS is controlled through investigating institutional relationships between innovation actors conducting NRDPs. It is based on the fact that the NRDPs were designed and operated by the various S&T policies and innovation actors related to new-drug R&D. Different responses by innovation actors to the NRDPs in terms of exploration practices are captured by drawing on the large-scale, long-term projects under the 21c Frontier Programme.

As the KoPI is characterised as a densely populated SME-led sector, the thesis draws on nine case firms to analyse firms' learning. These are the first-tier domestic firms that initiated new-drug development just after the introduction of the product patent system in 1987, and succeeded in developing their own NCEs or IMDs in the transitional phase.[68] They were selected as representative domestic companies with long-term experience in R&D and marketing of new drugs. In examining multiple cases, replication logic and complementary/comparative analysis between firms can potentially be achieved (in the application of Yin's multi-case study method (Yin 2003, pp. 49–51)).[69,70]

3.5.1.3 Dynamic view of the research issue

The research addresses the transitional phase by comparing the initial stage of new-drug R&D and the follow-up second round of new-drug R&D. In doing so, it tries to understand the long-term dynamics of the technological learning pattern, including the institutional and organisational factors that influence this pattern.

3.5.2 Methods of data collection

This sub-section briefly presents the methods of collecting data and the data gathered. There are two points concerning the process of data collection. First of all, the data were collected and further analysed while keeping in mind the concern with maintaining 'a chain of evidence' (Yin 2003, pp. 105-106). The data collection particularly considered the direct relevance between the original research issue, its theoretical and conceptual

[68] One R&D-intensive domestic company, SK Chemical, was excluded from the study due to the difficulty in collecting and clarifying data. This company is an affiliate of the SK Group, a *Chaebol,* and operates bio and pharmaceutical R&D as a business unit.

[69] Complementary analysis: That is, observation of nine firms can lead to the possibility of identifying variety (similarities/differences) in latecomer firms' transformation toward an innovation-generating firm.

[70] Observation of multi-case firms is likely to be more reflective in the many SME-led industries, such as KoPI, compared to monopolistic or oligopolistic industries. The latter industries are basically simpler than the former in terms of sampling and interpreting the sectoral change by focusing on one or two large companies. Thus, a few companies' innovation movements are easily treated as sectoral innovation (e.g. most of Korea's caught-up industries such as electronics, ICTs and automobiles), giving an impression of the industry as an autonomous entity itself.

framing in the two embedded units of analysis, and the data collected. Second, as many case studies carefully address, data collection was conducted to acquire a maximum level of data triangulation.

(i) Content of data collected

The data were collected to answer the research questions, drawing on the conceptual framework and its focus on the two dimensions of the analysis: the macro-level impact of policy on exploratory learning and micro-level firms' learning patterns. In terms of the macro-level dimension, data were gathered regarding the changing market selection environment and changed relationship between innovation actors in dealing with NRDPs under the S&T policy reform (Table 3.2). In terms of the firm-level perspective, data about new drug development processes and about relevant organisational processes of the nine case firms were collected (Table 3.3).

Table 3.2: Types of data about macro-level environmental conditions

Dimension of data		Types of data collected
Innovation systems	Market environment	· Institutional change: IPR regime and NHI system · Technological change: influence of biotechnology · Market data: Market segments and products
	NRDPs	· National S&T and industrial policies · Elements of innovation systems · NRDPs surrounding the KoPI and biotechnology
		· Relationship between innovation actors · Incentive structure and evaluation pattern

Table 3.3: Types of data about micro-level firms

Dimension of data		Types of data collected
Firms	R&D process	· History of case firms' R&D · New drug R&D processes · Commercialisation of new drugs developed · Patent/publication trend
	Organisational mechanism	· Organisational structure of R&D centre · Top management's response on new drug R&D · Organisational inertia and researchers' mindset

(ii) Methods of data collection

The data were collected mainly through three approaches: a) interviews, b) secondary data, and c) additional patent/publication information. Taking the three approaches was expected to provide at least a minimum level of reliability of the data (i.e., the convergence of the data). Moreover, attempts were made to secure the validity of the data by cross-checking the viewpoints of different types of concerned innovation actors on the patterns of institutional influence, technological learning and industrial transition.

In terms of interviews, both open-ended and semi-structured interviews were conducted during the two fieldwork periods (Table 3.4). The use of both types of interviews tended to generate unpredicted or more in-depth information as well as data that the fieldwork originally aimed to gather. Of the 55 interviews conducted, 44 were recorded; the remainder were conducted with note-taking due to the rules of the organisations and personal preference of the interviewees.

Table 3.4: Overview of interviews[71]

Fieldwork	Area of interviewee (No. of interviews)	Period
First round	13 Firms - DBFs and large firms (17) 6 GRIs (10) 5 Universities (5)	Aug, 2008 ~ Oct, 2008 Feb, 2009
Second round	7 Domestic pharmaceutical firms (14) 2 Big Pharma (2) 3DBFs (4)	Sep, 2010 ~ Oct, 2010
4 e-mail interviews and 2 anonymous interviewees		2010, 2011 and 2013

During the initial fieldwork, interviews were mainly conducted with people outside pharmaceutical firms, such as those at DBFs, universities and GRIs. The DBFs, universities and GRIs interviewed consisted of three categories. The first group were those who participated in long term NRDPs, mainly the three Frontier Programmes that included new drug R&D. The second group were those who had experience of public-private collaboration and technology transfer. It was aimed to complement the practical limitation between the public and private interaction in the three NRDPs.[72] The last group involved the policy and industry researchers of the pharmaceutical and biotechnological sectors, governmental officers, and researchers of Big Pharma, who previously experienced the KoPI or NRDPs. In doing so, data were expected to identify the overall

[71] See Appendix 2 for more details of the interviewees, and Appendices 3 and 4 for the questionnaire and survey.
[72] As will be seen, most NRDPs containing public and private actors have been conducted with few horizontal collaborations, rather in the way of sub-contractors.

institutional conditions surrounding the innovation activity in the KoPI and operational mechanisms of NRDPs.

The second round of fieldwork gathered data about the firms' exploratory learning involved in new drug R&D by focusing on the new drug development processes and strategies, and organisational perspectives. In addition, the data of the operational pattern of the NRDPs were also gathered in the view of the KoPI.

Most interviewees, including policy-side people, were junior and senior level PhD holders. This was due to the characteristics of the industry, which requires personnel with higher levels of scientific knowledge. For example, all project leaders of NRDPs, CEOs of DBFs and CTOs of pharmaceutical firms are PhD researchers. Herein, it should be noted that there was little need to interview young (PhD) researchers because the data collection focused on historical experiences of the transition and only the senior researchers had experienced the transitional period. Moreover, because the unit of the analysis was basically the firm and system levels and all companies that had operated small-sized R&D organisations, detailed investigation of the (short experience) individual researcher's behavioural pattern (at the lower levels of the organisational hierarchy) appeared to be unnecessary for this study.[73]

b) In terms of secondary data, all kinds of secondary data sources were used for data acquisition, ranging from the government, public and private institutes' policy reports, firms' annual reports and newspapers, to conference and exhibition attendance. In particular, two types of secondary data sources were unexpectedly useful. First were the web pages that stored video clips of interviews with people from industrial and academic biotechnology communities and the KoPI. These included researchers' in-depth comments about their professional communities.[74] Second, various industry-specific business newspapers provided complementary information of the NRDPs and case firms.[75]

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[73] In addition, conducting surveys was attempted during both fieldwork periods. However, the response rate was not meaningful and responses were mainly obtained from CEOs, CTOs or project leaders. As noted, because their R&D organisations were mostly small or medium sized, these respondents seemed to feel no need to circulate survey questionnaires to their researchers, as they made sure that they were aware of most critical R&D situations in the company as the representative respondents. As a result, the data gathered from the survey were not explicitly used for an empirical analysis, but were used as complementary data for the qualitative analysis and discussion.

[74] In the professional area of biotechnology, including pharmaceutical R&D in Korea, there has been a particularly influential cyber community (BRIC: Biological Research Information Center, http://bric.postech.ac.kr/). For example, the scientific fraud of stem cell research led by Dr Hwang's team was first raised and scientifically refuted by anonymous young and junior researchers in the cyber community.

[75] In total, 18 out of 24 pharmaceutical and health care specific business newspapers were used over the research period.

c) In terms of patent information, data for patent applications sent to the Korea Patent Office by the nine case firms, and their publication data acquired from Web of Science, were compared with qualitative data gathered regarding the exploration pattern. The patent and publication data were expected to provide the opportunity to confirm and complement the contents of interviews and qualitative data gathered from other sources.

3.5.3 Analysing the data

The collected data were analysed through two steps after the first and the second fieldwork sessions. As noted, the analysis after the first fieldwork focused on interpreting the operational mechanisms of NRDPs and the response of the four types of innovation actors to the operational pattern of NRDPs. The second main analysis (after the second fieldwork session) concentrated on interpreting the series of new drug R&D projects in each case firm in terms of learning process and strategy. The analysis also considered the underlying relationship between other private and public innovation actors and the pharmaceutical firms, and between the organisational change of R&D centres and the expansion of new drug R&D projects.

The data gathered were manually coded and analysed. First of all, the interview transcripts were re-described based on a timeline that went from the initial point to present status of the transition across two major categories of institutional and organisational dimensions. They were then rearranged based on the sub-categories in each dimension depending on the types of innovation actors. These innovation actors included pharmaceutical firms, GRIs and three ministries. The data related to exploratory learning, for each type of innovation actor, were then re-illustrated, connected and compared, drawing on a series of codes drawn on the one hand from the literature review and preliminary data, and on the other partly emerging from the interviews. These included ‘autonomous’ and ‘long-term’ technological learning, ‘the change of organisational structure’, ‘influence of project-based system (PBS) on research activities’, and ‘hidden conflicts between the pharmaceutical firms and DBFs’. The analysis enabled the research to identify the patterns of influencing that connect institutional and organisational factors to innovation actors’ exploratory learning.

Lastly, one analytical limitation should be pointed out. The macro-level analysis through NRDPs is conducted not by observing the operational pattern of a specific programme, but by investigating the operational patterns of several programmes relating to new drug R&D in a general context: the large-scale Frontier Programmes partly including new drug R&D combined with interviewees from outside of the three NRDPs. No NRDP conducted comprehensive upstream and downstream R&D steps; instead, most industrial actors

joined small-scale projects, often as contractors, or they received support for individual clinical development, thus imposing the general-level analysis of NRDPs.

3.6 Summary

This chapter established three axes for conducting the overall research: formulating the main research questions, developing conceptual and analytical frameworks and establishing a research methodology.

First, it formulated the research questions that deal with tracing the enhancement of the key mode of technological learning for transition, that is, exploratory learning. Based on the literature review, it was found that the overall rate of the transition of the KoPI is affected by the effectiveness of exploratory learning, and that exploratory learning is, in practice, influenced by institutional and organisational processes. Thus, it focused on developing research questions to understand how institutional and organisational mechanisms enhance exploratory learning.

Second, a conceptual framework was developed that takes a transformative view of institutional and organisational mechanisms that help latecomers' technological learning move from an exploitation-oriented to an exploration-oriented mode. The transformation of the institutional mechanisms was conceptualised in terms of the influence of rearranged S&T policies on the innovation actors' exploratory learning within the frame of an SIS. Organisational transformation at the firm level was conceptualised as a change in (R&D) exploratory practices and corresponding organisational processes.

The analytical framework was then laid out. At the innovation system level, NRDPs were introduced as the main analytical object. At the firm level, new-drug R&D processes in the first and second round were chosen to be examined.

Lastly, the overall methodology employed in this research was presented, and the advantages of the embedded single case study approach were discussed. Moreover, the scope of data collection and the overall process and limitation of data analysis were presented.

Chapter 4: Research context

4.1 Introduction

This chapter presents how the technological and institutional contexts surrounding the KoPI have changed over the last two decades, from a developing to a developed country's circumstances. On this basis, special attention is given to the changing market selection environment by the external institutional pressures such as IPR regime and NHI reform. It also pays attention to the changing S&T policies that directly affected technological learning patterns of innovation actors surrounding new-drug R&D.

In particular, these types of institutional and technical changes, such as the IPR regime, national health system, and biotechnology, are not unique to Korea but are also applicable to other developed or developing countries. What makes Korea's experience idiosyncratic is the country's subtle position between the A7[76] countries and the developing countries. It has experienced both groups' institutional and technological issues in the very compacted period of the 1980s onward.

To begin, this chapter describes the two basic perspectives of the pharmaceutical industry, namely the drug R&D process and the general market structure, in a global context (Section 4.2). This is followed by a presentation of the local institutional contexts (Section 4.3). Section 4.4 identifies changes in the market selection mechanism that have been shaped by those institutional pressures and that have, in turn, driven new-drug R&D. Section 4.5 presents the macro-level changes in S&T policies directly involving new-drug R&D of innovation actors. A summary section (Section 4.6) concludes the chapter.

4.2 Overview of the Pharmaceutical Industry

This part describes the overall process of drug development (Sub-section 4.2.1), as well as the general business model of a new drug in terms of its market life cycle (Sub-section 4.2.2). In particular, the view of latecomers underlying the explanation of both the drug R&D process and the business model is explored.

4.2.1 Technological context

[76] A7 countries, which have led the pharmaceutical industry, refer to the US, Japan, Germany, the UK, France, Italy and Switzerland.

New-drug R&D consists of both product and process development (Figure 4.1). Product development comprises four major steps often characterised as new-drug R&D. It involves the exploration of drug candidates, sophisticated tests for their reliability, and the development of a specific formulation. Process development, in contrast, involves the efficient synthesis and qualitative production of the new drug. This section briefly illustrates the main technological activities of each of the R&D steps.

4.2.1.1 Product development

1) Step 1 – Drug discovery

This first step has two main goals: selecting the biochemical target and developing drug candidates that act on that target. The former includes two research activities: i) target identification, and ii) target validation. The latter includes two more activities: iii) lead identification, and iv) lead optimisation.

i. Targets that intervene in a process of disease expression (i.e., promote or block) are identified at various levels such as the receptor, biochemical pathway, and further gene levels.
ii. The target candidates should then be validated to confirm whether they are 'druggable'. Only a few targets can be shown to be druggable, by proving effective bonding with the molecules of the disease. This process requires long-term experiments that should show a statistically significant relationship between disease expression and the presence of the target candidate (Pisano 2006).[77]

This initial research, (i) and (ii), substantiates the concept of the potential drug to be developed by understanding the relationship between disease expression and the target candidate. They are the most upstream scientific research part of the whole drug R&D steps.

iii. Based on the target selected, an attempt is made to develop a few lead compounds that can inhibit the binding of the disease molecules with the identified target. This involves synthesis and screening of thousands of molecules (about 10,000 compounds: Pisano 1997) to search potential drug candidates ('hits'). The drug candidates that structurally bind to the target with the expected degree of activity are selected as the lead compounds. This process involves repetitively collaborative long-lasting research between chemists and biologists. Given biochemical information about the target from a biologist, a chemist

[77] The process is typically conducted through the use of a disease model using 'knock-out' mice. The term knock-out (knock-in) mice means experimental mice that are genetically manipulated to underexpress (overexpress) the target candidate.

synthesises a series of structurally modified molecules, then the biologist observes the response, the activity of disease expression, in the disease model.

iv. However, the lead compound cannot be the final drug candidate without further optimisation. To do this, several derivatives based on the lead compound are synthesised and tested experimentally in an animal model to find the best-fitting compound for the target and the most effective characteristics as a medicine (Pisano 2006). In this process of discovery research, which usually takes about two to five years, a few drug candidates are developed.

This drug discovery stage is regarded as the upstream side of the whole drug R&D chain. These scientific experiments are often conducted by public actors such as universities because these stages are the explorative and discovery-oriented, particularly in the stages of target identification and validation and lead identification. Of course, exploratory R&D by pharmaceutical firms also begins in this stage. Due to the broad range of diseases and the variety of levels of biological mechanisms, from gene to symptom expression, the upstream research is extensively fragmented across the laboratories of universities, GRIs, DBFs and pharmaceutical firms in the world.

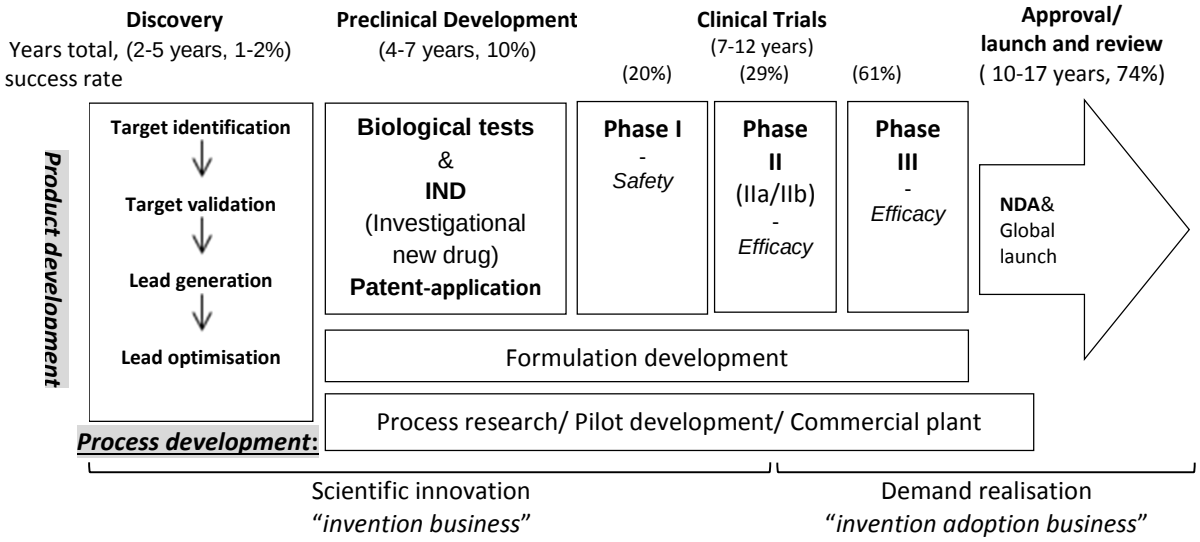

Figure 4.1: The process of new-drug R&D

Source: Based on Di Masi and Grabowski (2007), Burns (2005), and Drews (2000)

2) Emergence of a new-drug business model

Key product patents (i.e., the lead compound and its further derivatives), and patents for the composition of matter of NCEs, are generated during the lead identification and optimisation steps. These patents are regarded as the most vital and valuable commercially (Burns 2005), as 20 years of exclusive sales are guaranteed. As the

patented drug candidate requires further testing in preclinical and clinical trials, the real period of protection in the market is closer to around 10 years. This product patent is the fundamental basis for the new-drug-driven business model of Big Pharma.

In the drug discovery process, two types of new drugs are identified. First, if a new drug is developed based on the identification of a new target or biochemical mechanism, it is generally referred to as the **first-in-class** drug, or **innovative** new drug. Second, if a new drug is developed based on the modification of the existing lead compound of an innovative new drug, it is classified as a follow-on new drug, aiming at being a **me-too, me-better** or **best-in-class** drug.

3) Step 2 - Preclinical development

As a subsequent step, preclinical development with animal tests is necessary to check the toxicity, potential effectiveness, and biochemical processing of the derivative (i.e., the drug candidate), prior to proceeding to clinical trials in humans, due to safety and effectiveness issues (Pisano 2006).[78] A most promising candidate and a few 'back-up' candidates are chosen in this step (*ibid*). This takes one year, and the firm submits the investigational new drug (IND) details, with all the data collected about the preclinical tests, to the regulatory authorities, such as the FDA, to secure permission to conduct clinical trials in humans (Burns 2005). That is, new-drug R&D is highly regulated in the R&D stage, unlike most other industries.

4) Step 3 - Clinical trials

The clinical trials of the drug candidate commence to evaluate the toxicity (safety) and efficacy in humans after the approval of the IND. As safety is prioritised ahead of efficacy, a **phase 1** trial is conducted to confirm safety within a small sample of volunteers (about 20 to 100) (*ibid*). This generally takes one and a half years (Paul et al. 2010). If the safety criteria are met, then the second phase of the clinical trial is performed. In particular, the second phase proceeds with two sequential steps: phase 2a and 2b.

Phase 2a is concerned with investigating the efficacy of various dosages and corresponding side effects (*ibid*). That is, phase 2a is the pilot study that evaluates safety and checks efficacy. In contrast, **phase 2b**, called the pivotal study, is conducted to demonstrate efficacy and to determine the optimal therapeutic dosages and the best type of formulation. In particular, this stage is conducted in strict compliance with regulatory guidelines. The completion of phase 2 indicates an increased probability of final success,

[78] The investigation of biochemical processing is referred to as ADME studies (Absorption, Distribution, Metabolism, and Excretion of the derivatives).

to a rate of about 30-60%; therefore, it is regarded as the '*major fulcrum of value* in the development part of the value chain' (Burns 2005: 61-64).

Phase 3 is to confirm the long-term efficacy and safety through confirmation of statistical significance and comparison with rival drugs (Burns 2005). Thus, phase 3 normally needs a large number of patients from multiple sites for the clinical trial (for the global launch, about 1,000 to 5,000 patients). This phase takes approximately two and a half years and costs about $235 million (Paul et al. 2010). As the entry into phase 3 signifies a higher probability of a successful market launch of the drug candidate, this process, in many respects, is regarded as the initial phase of commercialisation rather than the final stage of the development process (Burns 2005: 64-65). That is, this phase involves showing evidence of overall specifications and clinical benefits (efficacy and safety) of the drug candidate to stakeholders such as regulatory authorities in various nations, prescribers and final consumers (*ibid*).

5) Step 4 – Approval and global launch

Acquisition of NDA approval requires that all data for the clinical results and drug information be analysed and submitted to the regulatory authority, such as the US FDA or the European Medicines Agency. The preparation of the NDA also requires significant levels of documentation and the preparation of responses to questions from the FDA (Burns 2005: 65-66). With the review by the FDA taking a year, the NDA is approved with particular specifications (e.g., dosage form, amount, substantial efficacy and potential side effects) (Pisano 2006). In general, this takes about one and a half years, including the review (in the case of the US), and costs about $40 million (Paul et al. 2010).

4.2.1.2 Process development

In parallel with the product development steps, process R&D is also necessary to develop an efficient synthesis route and commercial production. The real process research concerned with commercial production starts in preclinical development (Pisano 1997).[79] Devising the most commercially efficient (with simpler reaction steps) and technologically effective (with higher purity and stable reaction steps) method of synthesis, and its scale-up, becomes the main goal of process development (Table 4.1). Additionally, the optimal synthesis route for the chosen type of formulation (e.g., tablet, injection, capsule, or patch) should be decided. This process development is generally completed in parallel with the phase 2 clinical trial (Figure 4.1).

[79] Although the initial synthesis method for the candidate compound is devised in the discovery step, it is seen as a discovery process rather than process research for developing the synthesis route for commercial production.

Moreover, this process development is a critical R&D stage in producing biological drugs because of the technological difficulty of controlling the whole processes of organically high-molecular characteristics and maintaining the yield rate of the production at the same quality. Thus, process development becomes vital, even in a copy version of original biologics. As noted, it is attributed to the low level of engineering in integrality-based biological drugs. That is why the copy of original biologics is called a “bio-similar”, not a “bio-copy” or “bio-generics”.

Table 4.1: Key perspectives of the process development

	Initial discovery process	Final commercial production process
Number of chemical steps	25	7
Equipment	Test tubes; 1-liter flasks	2,000-4,000 gallon stainless steel vessels
Batch size (output)	~1 gram	100 ~ 200 kg
Operators	PhD chemists	Technicians; semiskilled plant workers
Purity	1%-10%	99.9%
Cost per kilogram	~ $20,000-$50,000/kg	~$3,500/kg
Criteria for process design	Biological activity of molecule; patent issues	Cost; quality (purity); conformance with drug and environmental protection regulations; operability

Source: Pisano (1997: p.121)

4.2.1.3 Latecomers’ approach

It is worth noting the application of the reversed PLC cycle in the pharmaceutical industry. As seen briefly, based on the case of the KoPI, technological accumulation in the latecomers’ pharmaceutical industry also seems to follow the overall trajectory of the reversed PLC (Figure 4.2). The latecomer pharmaceutical firms start to accumulate technological capability initially by establishing production capability, then by developing generic drugs, focusing on synthetic and formulation technologies, and finally by trying to develop their own new drugs.

However, what makes the stepwise industrial catch-up in the industry more difficult is primarily rooted in the product patent barrier and in scientific research capability. Once new drug material acquires a product patent, there is legal prevention of copying the drug by latecomers for 20 years (in general 10 years after market launch) (Figure 4.2).

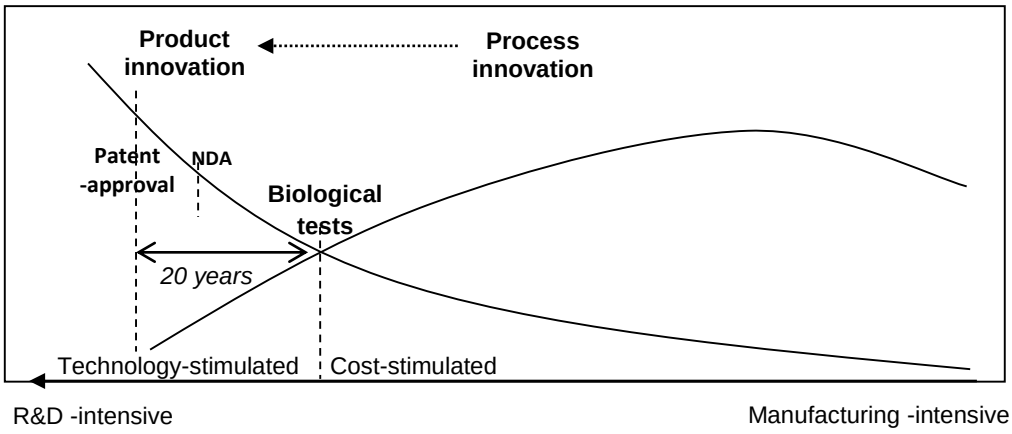

Figure 4.2: Technological catch-up pattern reversing the PLC

Source: own elaboration based on the PLC model

Thus, even though latecomers can master the production and synthetic technologies of the material (i.e., process development), they are not allowed to penetrate the market. Furthermore, mastering the process technologies never guarantees the scientific research capability that allows drug discovery. The latter capability is only accumulated through long-term and high-risk internal and upstream research, as in advanced firms.

Summing up, for latecomers mostly focusing on imitative production, the product patent means the forestalling of copying for 20 years, even though the technological specifications of drugs are open to the public through publication and patent. Thus, the product patent regime has made the pharmaceutical market clearly separated between the high-value-added new-drug market, mainly based on exploratory learning and protected by the patent system, and the cost-competitive generic-drug market, based on exploitive learning and possible only after the expiration of the patent.

4.2.1.4 Decreasing R&D productivity

In spite of the benefit of new technologies and sciences, R&D productivity in new drug development has noticeably decreased. The annual number of applications for new molecular entities (NMEs) to the US FDA has continuously decreased for the last two decades (Figure 4.3). Consequently, the number of NDA approvals of NMEs has decreased from an average annual number of 36 between 1995 and 2004 to 22 between 2005 and 2010 (Dubin 2012). In contrast, annual R&D expenditures, in the example of the PhRMA member firms (including most Big Pharma companies), has sharply increased, by almost four-fold over the last 20 years (to $48.5 billion in 2007 from $11.5

billion in 1992).[80] Overall, it is apparent that R&D productivity in the industry has worsened; a phenomenon referred to as the 'innovation gap'.

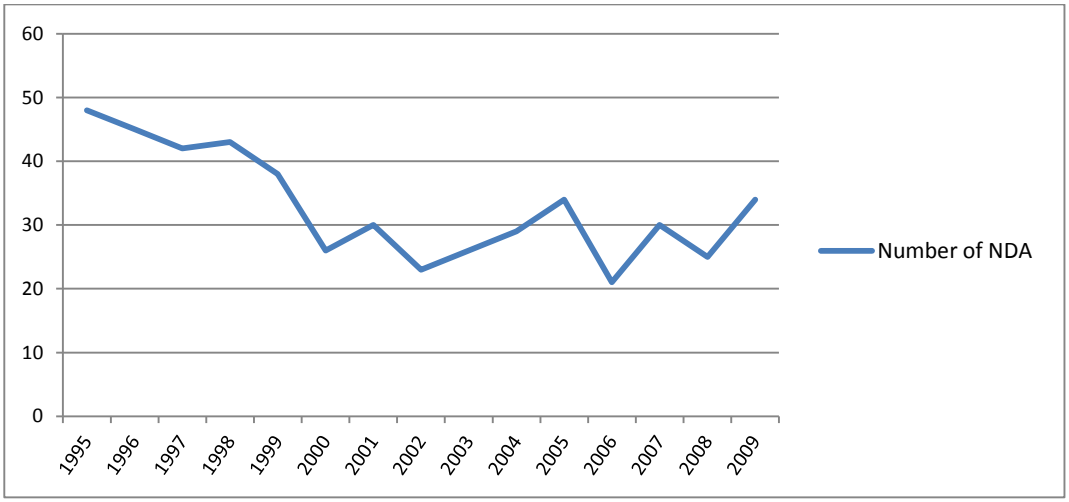

Figure 4.3: Annual number of NDA filed with the US FDA

Source: Parexel White Paper (2010)

Although they are not easily ascertained, both technological and institutional factors of this decreasing productivity have been identified. First of all, in terms of technology, new drug development through identifying novel targets instead of concentrating on known targets has increased the uncertainty of discovery and clinical development (Hu et al. 2007). That is, opting for more novel targets means that clinical development becomes riskier. This technological pressure seems to be largely attributable to the previously successful era of new drug development and a resulting saturation of available known targets (Booth and Zemmel 2004, Hu et al. 2007, Dubin 2012).[81]

Consequently, the relative abundance of drugs presently being marketed, and the incomplete understanding of biological mechanisms, has resulted in intensified institutional demand for clinical differentiation by the FDA and has made extensive and large-scale clinical trials necessary (LaMattina 2012). As a result, pharmaceutical firms have been forced to take more novel approaches with safer and more effective specifications than for the presently dominant drugs. Between 2007 and 2010, the failure rate of phase 3 and NDA increased rapidly, to almost 50% (83 projects) (Arrowsmith 2011).

[80] Meanwhile, the number of NDAs by the member firms decreased from 26 to 19.
[81] Moreover, as pointed out, the scientific advances in understanding of the biochemical mechanisms are still underway, resting somewhere between empiricism and engineering.

4.2.2 Market context

In 2009, global pharmaceutical sales reached $800 billion, doubling in just seven years (from about $400 billion in 2002), led by Big Pharma (Table 4.2). In particular, the concentration of the top ten sales companies intensified from 29% to 45% over the same period. Meanwhile, the generic drug market has grown to about 10% of the global market share in terms of sales size.

Table 4.2: Sales size of Big Pharma in 1990 and 2009 (US$ billions)[82]

	Company (in 1990)	Sales	Share	Company (in 2009)	Sales	Share
1	Merck	5.7	3.8%	Pfizer*	57.0	7.6%
2	Bristol/Squibb	5.3	3.5%	Merck & Co (MSD)	39.0	5.2%
3	Glaxo	5.2	3.3%	Novartis*	38.5	5.1%
4	Johnson & Johnson	4.5	3.0%	Sanofi-Aventis*	35.5	4.7%
5	Smith Kline Beecham	4.3	2.9%	GSK *	35.0	4.7%
6	Ciba-Geigy	4.2	2.8%	AstraZeneca	34.4	4.6%
7	American Home Product	3.9	2.6%	Roche	32.8	4.4%
8	Hoechst	3.8	2.6%	Johnson & Johnson	26.8	3.6%
9	Lilly	3.7	2.5%	Lilly	20.3	2.7%
10	Bayer	3.3	2.2%	Abbott	19.8	2.6%
11	Roche	3.2	2.2%	Teva	15.9	2.1%
12	Pfizer	3.2	2.2%	Bayer	15.7	2.1%
13	Sandoz	3.2	2.2%	Boehringer Ingel	15.3	2.0%
14	Rhone Poulenc	3.2	2.1%	Amgen	15.0	2.0%
15	Upjohn	2.4	1.6%	Takeda	14.4	1.9%
Total		59.1	39.5%		415.4	55.3%

Source: Various sources on the global pharmaceutical industry

4.2.2.1 Conventional business model: Branded new drugs and generic drugs

The pharmaceutical market is divided into two product categories, new drugs and generic drugs, and is concerned with the PLC of drugs in the same class (indication or therapeutic area). To begin with, as the first drug developed in a therapeutic area, the launch of the 'first-in-class' drug (i.e., innovative new drug) initiates the PLC (A in Figure 4.4). New drugs follow, with improved safety or efficacy, developed by competing companies and often based on the same lead compound but with considerable modification of the chemical structure, i.e., 'me-too/me-better/best-in-class' drugs (B in Figure 4.4). These still require full-scale clinical trials and NDA approval. These drugs

[82] Pfizer: Pfizer, Warner-Lambert, and Pharmacia; Novartis: Ciba-Geigy and Sandoz; GSK: Glaxo, Wellcome and Smith Kline Beecham; Sanofi-Aventis: Sanofi, Hoechst, and Rhone Poulenc.

are referred to as 'branded' drugs. In general, industry leadership has been based on these branded and patented drugs.

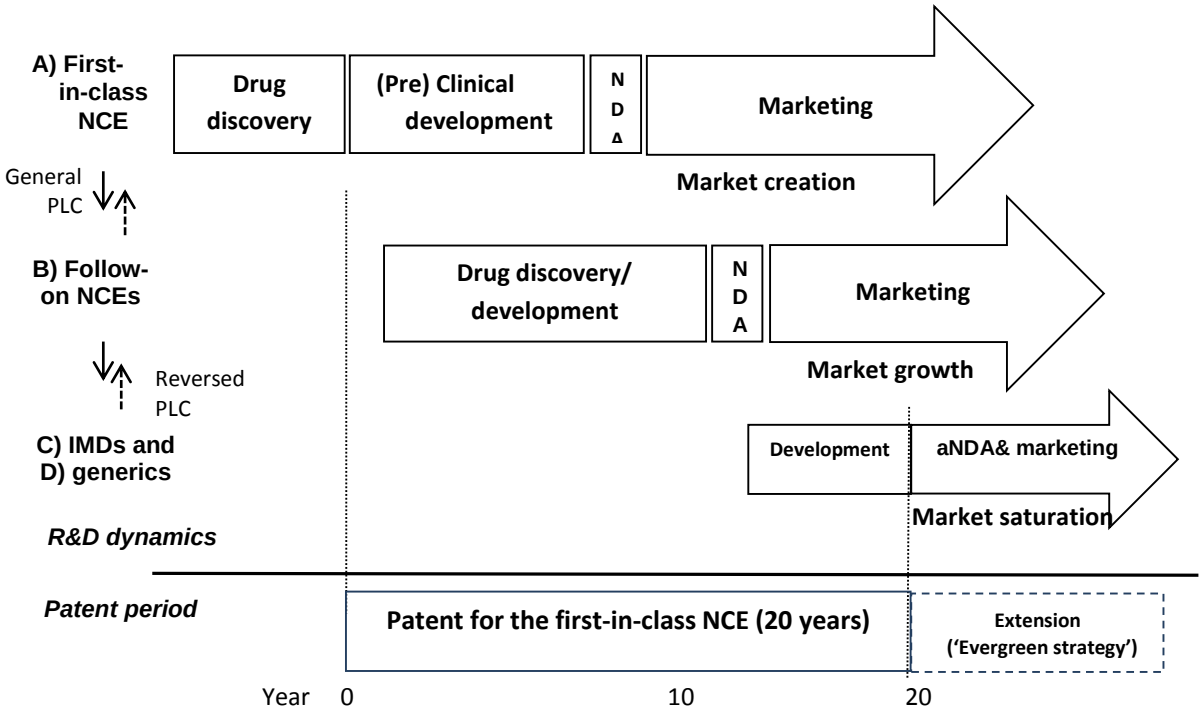

Figure 4.4: The market life cycle of drugs in a class

Source: Own elaboration based on various sources

The product patents of these new drugs expire after 20 years of exclusivity. Then, a new rule of market competition emerges, based on cost efficiency and time to market (C and D in Figure 4.4). These off-patent generic drugs and incrementally modified drugs (IMDs), partially patented, are developed mainly through process development, i.e., alternative synthesis routes of the original drugs (Sub-section 4.2.1.2). They are approved through bioequivalence tests or aNDA (abbreviated NDA) that exempt the drugs from full-scale implementation of clinical trials. These drugs compete with other generic drugs based on cost and time to market.

In terms of the new drug market, between 1950 and 2008 1,222 new drugs (i.e., new chemical and biological drugs) were approved by the US FDA (Munos 2009). Interestingly, 21 companies accounted for half the new drugs and only half those companies have survived (Munos 2009).[83]

[83] For example, Merck developed almost 60 new drugs, followed by Lilly, Roche, and Pfizer (each about 50 new drugs). Moreover, the fluctuation of the ranks between 1990 and 2009 is, at first glance, attributed to the outcome of new drug launch as well as M&A. For example, Pfizer, Novartis, Sanofi-Aventis, and Roche have developed 13, 11, 8, and 10 new drugs, respectively, between 2000 and 2007 (Pammolli et al. 2011), leading to their industrial leadership (Table 4.3)

From the view of latecomer firms, it is noticeable that the pharmaceutical industry has not allowed latecomers to take over the market or to take technological leadership until now. All the top ten Big Pharma are located in the US and a few European countries, i.e., mainly in A7 countries.

Meanwhile, the global generic drug market also rapidly grew in the 2000s, accounting for about $80 billion in 2009, compared to less than $50 billion in 2004. Traditionally, the major demand for generic drugs came from developing countries, which have weak purchasing power for new drugs (Dubey and Dubey 2009). However, the Hatch-Waxman Act in 1984 considerably lowered the entry barrier to the US market for generic drug producers.[84] This Act aimed to reduce national medication costs. Since then, generic drugs have increasingly taken the majority of the largest pharmaceutical markets, reaching 78% of the total number of prescriptions in 2010 from 19% in 1984 (von Koeckritz 2012).

In reality, institutional change has provided the generic drug developers with a new market opportunity, which has been regarded as a potential threat to the profit source of the new-drug-based Big Pharma. Specifically, since the technological source of the generic drug business is based on technological accumulation in process development, this lower technological requirement has allowed domestic and overseas generic drug developers to penetrate the US market. Core capabilities are involved in the rapid development and market launch of generic drugs through reverse engineering and acquisition of production standards, such as Current Good Manufacturing Practice (cGMP), by the US FDA. The recent successful entry into the US market by Indian pharmaceutical companies signifies the possibility of market catch-up through exploitive technological learning.

Table 4.3: Classification of drugs

		Technological base	
		Chemical synthesis	Biological development
Degree of innovation	Innovative (created)	・NCEs (chemistry-based) ・Phytomedicines (plant-based)	・Biologics (biological new-drugs)
	Imitative(modified)	・IMDs	・Biobetters
	Imitative (copied)	・Generics	・Biosimilars

Source: Own elaboration based on various sources

[84] This act removed the need for conducting full scale clinical trials of generic drugs, replacing these trials with short-term bioequivalence tests.

4.2.2.2 Changing business model: The emerging niche markets

Under sharpening innovation pressure resulting from technological and institutional changes, the conventional business model, which polarised pharmaceuticals into two dichotomised markets, seems to be changing. The current, more complicated, state of affairs has led to the emergence of niche markets (Table 4.3). Basically, the emerging niche market seems to be an interactive and strategic response both from Big Pharma and generic drug producers in dealing with technological and institutional changes.

With respect to the new-drug-based Big Pharma, and based on the literature review four types of responses are observed in parallel with maintaining internal new-drug R&D:

- '*Ever-greening strategy*': Companies have tried to extend the period and scope of patent protection by acquiring multiple peripheral patents embracing various aspects of the original product patent, referred to as an 'ever-greening strategy' (Thomas 2009). In doing so, they intend to delay the entry of subsequent generic drugs.
- *IMDs*: Product differentiation based on the original drug is articulated to extend the life cycle of the original drug, constantly surpassing rival new drugs and generics. IMDs such as combination drugs have been observed.
- *Entry to the generic drug market*: In the increasing market size of generic drugs, both in the home countries of Big Pharma and in emerging markets, companies have entered the generic drug market by acquiring local generic drug producers or making alliances.
- *Open innovation*: The outsourcing of potential targets and drug candidates has intensified and often deals with the view of 'open innovation'. This point indicates that even Big Pharma companies cannot conduct all of the necessary research within their R&D organisations in the rapidly broadening and deepening scientific knowledge bases of new drug R&D in the emerging biotechnology paradigm.

In the view of the generic-drugs-based latecomers, in general, they face both threats and opportunities in coping with their changing industrial environment:

- *Generic drug based global market penetration*: First of all, some latecomer firms have clearly taken new opportunities with the expanding generic drug market in advanced countries. The grasping of this opportunity requires mastery of production capability and managerial/marketing capability to enter the overseas advanced market.

- *IMD strategy*: In contrast, they also face strengthened patent pressures from the ever-greening strategy of NCEs and other trade policies linked to the IPR regime. To cope with the IPR regime, they have tried to bypass the patent based on technological modifications.
- *Impact of open innovation and new technological paradigm*: Like other emerging opportunities, presumably, the outsourcing trend of drug candidates in Big Pharma, open innovation, and the new technological paradigm of the biotechnology might positively affect the transitional dynamics from generic drug producers to new drug developers.

As mentioned, the environment for the transition of the KoPI in the last two decades has been influenced by global technological and institutional changes. In this context, the influence of the global industrial context on the local environment, and thus on the transitional catch-up, needs to be addressed in addition to the nation-specific institutional context of the KoPI. The following section deals with this perspective.

4.3 Institutional Environment of the KoPI

This section addresses the local institutional and technological background for the last 25 years' transition. First, it briefly presents the accumulation of production capability before entering into the transitional period (Subsection 4.3.1). Then, it describes the two major external institutional pressures that have ignited and accelerated the transition: the introduction of the product patent system as an initial version of TRIPS, and the reform of the NHI (Sub-section 4.3.2). It then describes the macro level industrial and S&T policy landscape that has directly affected the pattern of new-drug R&D by innovation actors (Sub-section 4.3.3).

4.3.1 Mastering imitative technologies in the 1970s

The real take-off of technological learning in the pharmaceutical industry was driven by a governmental policy in the 1960s to substitute active pharmaceutical ingredients (APIs). Because of the enormous trade deficit in the industry (Park 1990), the import substitution of pharmaceutical materials became one of the most critical issues in any industry.[85] The initial strategy was to setup joint ventures (JVs) for achieving local production.[86] The

[85] In 1960, the total amount of import of drugs including APIs, about US$5.26 million, accounted for 26% of the GNP. At the time, technological imports were strongly administered by government policy to regulate the outflow of foreign exchange (i.e., dollars) as noted above (KPMA 2005).
[86] Under the promotion act for introducing foreign capital, seven joint venture companies were organised, such as Handok (with German Hoechst, 1964), Kukje (with Italian Lepetit, 1959), Korea Schering (1967), Korea Pfizer (1969), and Korea Upjohn (1969).

pharmaceutical sector was the first industry that tried to absorb foreign technologies through JVs and technological transfer with advanced foreign companies in Korea (KPMA 1995).

In the 1970s, the ISI was intensified by institutionally guaranteeing domestic companies the exclusive rights to monopolise localised APIs for a certain preferential period (KPMA 2005). The government prohibited the import of raw materials developed by domestic companies for three years. Competing companies producing the same finished drugs had to purchase the API from the first domestic developer, as the import of APIs was banned.

Under the industrial policy, domestic pharmaceutical companies focused primarily on developing alternative synthetic routes. As a result, the ISI strategy, with an incentive system for technological learning, led to the assimilation of the fundamental synthetic and production capability, which are prerequisites for further imitative and innovative R&D activities (Figure 4.5).[87] It should be noted that the pharmaceutical companies were more attracted by the rapid growth of the domestic market than by exploiting overseas markets.

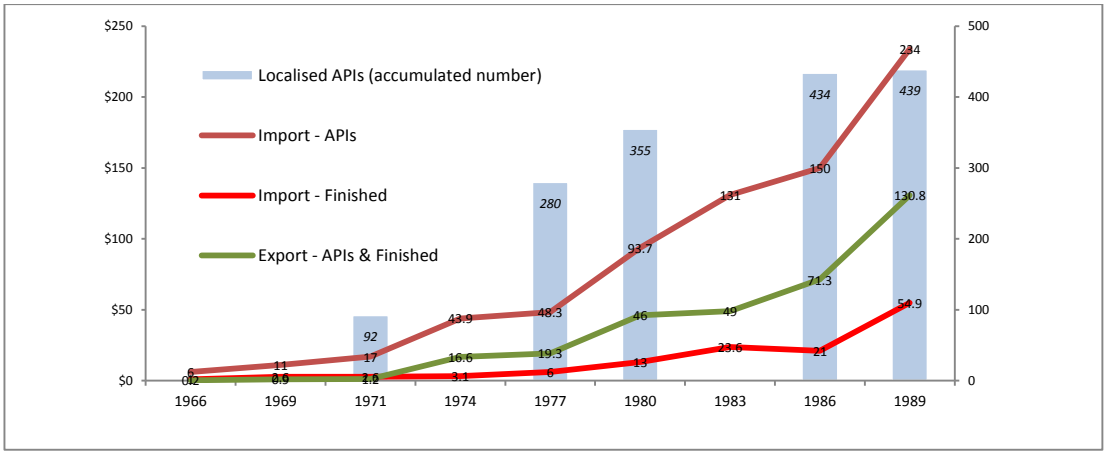

Figure 4.5 Import and export trend in the pharmaceutical industry **unit: million $**

Source: Reformation from KPTA Statistics, 1987

4.3.2 Major institutional changes

While the initial technological accumulation was successful, based on the duplicative imitation under the active market protection, the industrial environment has shown considerable turbulence since the 1980s. The introduction of the substance (product)

[87] The ISI strategy was operated with a link system between export and import; therefore, the importer had to export corresponding amounts of materials or finished products (Ahn 1991). This especially affected the import and export of oriental medicine materials (*ibid*).

patent became the initiator of the transition (Sub-section 4.3.2.1), and the reform of the NHI has accelerated the transitional effort (Sub-section 4.3.2.2).

4.3.2.1 Reinforcement of product patent in 1987

At the beginning of the 1980s, the US started to force some developing countries, such as Hungary, Mexico, Singapore, Taiwan and Korea, to strengthen their IPR regimes (e.g., product patents, trademarks and copyrights) (Nam 2006b). This was a period of reshaping the economic relationship between the US and Korea, as Korea had rapidly increased its exports to the US, while the US economy was stuck with so-called twin deficits in the first half of the 1980s (*ibid.*).

Under pressure, the Korean government decided in 1986 to introduce a new patent system, which took effect in 1987. The scope of the substance patent included newly synthesised chemical materials as well as 'invented' micro-organisms, vectors, natural substances, recombinant genes and cell lines, which had not previously been patentable in Korea. This became the first practical link between the international trade policy of the US and IPR issues (*ibid.*).

Although the accommodation of the product patent system seemed to be unavoidable for Korea at that time since the economic growth of the country was based on exports, many to the US (Park 1994),[88] the KoPI still saw it as too radical, in that it was immediately enforced the following year, 1987, without any grace period and with excessive accommodation of so-called 'pipeline products'.[89,90] In addition, the protection period of the patent was extended from 12 to 15 years, and then extended again to 20

[88] In retrospect, the pharmaceutical industry and other precision chemical industries, which had received little attention compared with heavy chemical industries (HCIs), became the scapegoats of international trade in order to bypass the trade offensive from the US and save the export-oriented leading industries of Korea (Park 1994). Under this political economic pretext, in 1985 the Reagan administration of the US instructed the United States Trade Representatives (USTR) to investigate the actual state of the protection of IPR in Korea, alluding to the possibility of execution of the Super 301 bill, which would lead to the restriction of exports to the US (Nam 2006a). In the trade talks, USTR raised the IPR issues of Korea, such as the scope and degree of copyrights and the introduction of substance patents. Korea became the first country to which the Super 301 bill of the USTR was applied.

[89] The government agreed with the application of the product patent retroactive to 1981. Therefore, all substance patents that were registered in the USPTO after 1980, but not yet launched as products in the US or Korean markets, could be protected in Korea. These products were called "pipeline products". This generally concerned pipeline products between the patent registration and the authorisation of new drugs by the US FDA. A total of 515 substance patents were protected as pipeline products by 1997, and domestic companies could not manufacture these drugs by 1997.

[90] The year of the introduction of the product patent system: the US (year of introduction of the substance patent: 1790), the UK (1949), West Germany (1968) and France (1969). For example, Japan enforced the substance patent system in 1976, 25 years after the issue was first posed. By 1976, 86 new NCEs had already been developed by Japanese domestic companies. Moreover, many late-industrialising countries, such as Italy, Spain, Mexico, Brazil and Norway, had not adopted a substance patent by that time.

years in 1996 by TRIPS. The same agreements with the EU and Japan were made in the early 1990s.

As a result, the introduction of substance patents blocked the duplicative imitation of the patented original drug. This led directly to changes in the rules of the game of domestic market competition and technological learning, in combination with liberalisation of the commodity and capital markets in the 1980s and 1990s. Prior to the introduction of the substance patent system, Korea had only admitted manufacturing process-related patents, so domestic companies could produce the same substances (drugs) if they proved some technological difference in the synthesis process.

As a result, the introduction of substance patents in Korea became a turning point that ignited an exploratory mode of technological learning for developing new drugs, although the copying and imitation strategy still echoed around the industry until at least the end of the 1990s. The CTO of Dong-a pointed out that substance patents led the industry to take on new-drug R&D (Interview 57 (K-Pharma)). That is, the product patent system became the 'push factor' for domestic firms to conduct exploratory learning.

4.3.2.2 Reform of national health insurance in 2000

The national health insurance system established in 1977 was fully reformed between 1999 and 2001 across three dimensions: financing of NHI, pharmaceuticals, and drug price reimbursement (Kwon and Reich 2005).[91] First, in 1999, all 350 insurance societies were integrated into a single payer, the National Health Insurance Corporation (NHIC). Second, the separation of prescribing and dispensing drugs between physicians and chemists (SPD) was enforced in 2000. Lastly, the criteria for drug price reimbursement were changed in 2001 to curtail the expenditures of the NHI.

In particular, the reinforcement of SPD and changes in the criteria for drug price reimbursement directly affected the pharmaceutical industry. Prior to the implementation of SPD, chemists were able to arbitrarily prescribe drugs for some common diseases, whilst after its implementation they were no longer allowed to do this. Moreover, the main criterion for drug price reimbursement was changed from the officially notified price (ONP) to the actual transaction price.[92] The actual transaction price system was regarded as

[91] The progressive new government tried to reform the economic system and strengthen social welfare systems, e.g., the enhancement of the public healthcare system and the reform of *Chaebol*-based economic growth.

[92] The ONP, which was determined by the composite of the ex-factory price, a fixed wholesale margin and VAT (value-added tax) supervised by a drug pricing commission of NHI, was used for pharmaceutical reimbursement (Chung and Kim 2005). The setting up of a fixed price for the ONP was intended to apply an identical repayment price (the price for reimbursement) to all hospitals and clinics (Kim and Choi 2002). The

being able to lower the economic margin of pharmaceutical firms below that of the ONP. The actual transaction price system was based on the lowest transaction price examined between the pharmaceutical firms and medical service providers as the price of the drug reimbursement.

In addition, the drug reimbursement scheme became more favourable towards imported new drugs (branded original drugs from Big Pharma). Imported drugs could be listed without restrictions in the drug reimbursement scheme. Prior to 2000, there had been non-tariff barriers to the import of new drugs to prevent multinational companies from direct entry to the domestic market; these barriers included the reimplementation of some clinical tests, the removal of imported drugs from the reimbursement list,[93] and the establishment of production factories in Korea (Rozek and Berkowitz 1998).[94] [95]

Overall, the NHI reforms led to a change in the structure of the domestic market that further implies a change in the technological learning. The following section discusses this change in market structure.

4.4 Changing Market Selection Criteria

This section examines the change in the market selection environment in the KoPI over the 25-year transitional period. This change was driven by the institutional pressures described above. In the first period of the transition, between 1987 and 1999, the market selection environment was shaped by the combined outcome of the implementation of the product patent system and the loose operation of NHI. In the on-going second period of the transition after 2000, the reform of NHI sharply changed the domestic market toward ETC drug-centred competition and cost curtailment of NHI.

4.4.1 Prior to the reform of NHI

After the reinforcement of the product patent system, copying original drugs without licensing was no longer a viable business model. Instead, local companies grappled with how to strengthen the development of OTC drugs and the licensed-in drug business

ONP of a drug first registered served as the benchmark price for other follow-up drugs with the same constituents, i.e., the same API.

[93] Thus, the medical providers had to apply the reimbursement of dispensing imported drugs one by one and pricing was done on a case by case basis.

[94] It should be noted that this research was supported by the representative US industrial association, PHRMA. The elimination of institutional discrimination continuously demanded by the US was mostly accepted in the reform of 1999 (ChosunIlbo 16/5/1999).

[95] The pricing criteria for imported drugs were also changed in a favourable way. The reimbursement price of imported drugs was set at the average price in the A7 countries, allowing higher pricing for imported drugs in the Korean market than in some A7 countries (Chung and Kim 2005). A7 countries: the US, Japan, Germany, the UK, France, Italy and Switzerland.

through alliances with Big Pharma and Japanese companies. Domestic firms, facing an unfriendly pricing policy for imported new drugs, made room for brokering the domestic market and Big Pharma through licensed-in drug production. OTC and domestically produced licensed-in drugs became critical sources of success in the domestic market until the reform of NHI in 2000.[96]

Along these lines, market competition occurred mainly through marketing capability rather than technological innovation. The problem was the considerable technological homogeneity of drugs between the domestic firms. Under intense competition, they tried to supply drugs at a discounted price to the healthcare service providers, while also attempting to maintain a higher ONP.[97] As a result, they were attracted to not only an official marketing channel, but also private networks to win over the physicians and chemists. This frequently led to dumping and illegal marketing activities such as bribing hospitals, clinics and chemist shops. It was the main mode of marketing by the pharmaceutical companies before 1999.

Overall, due to the limited technological capability to develop new drugs, the expansion of the NHI with a loose drug evaluation system led to the distortion of the micro-level market selection mechanism, forcing domestic firms to concentrate on marketing activities. Although the product patent system clearly stimulated new-drug R&D among domestic companies, technological capability scarcely influenced market selection at that time.

4.4.2 After the reform of the NHI

As stated, the SPD and the new actual transaction price system were enacted in 2000. The reform was regarded as a substantial threat by domestic pharmaceutical firms, as they had to change their marketing and technological learning patterns.

Two noticeable changes in the market selection environment were observed: (a) a reversal of the proportion between OTC drugs and ETC drugs, and (b) the increase in market share of Big Pharma (Figure 4.6).

[96] OTC drugs accounted for 58.6% of the domestic market in 1991.
[97] The lowered ONP meant a decrease in profit for the pharmaceutical firms. Thus, the higher the gap between ONP and the real transaction price they charged the healthcare service providers, the more profit they were guaranteed.

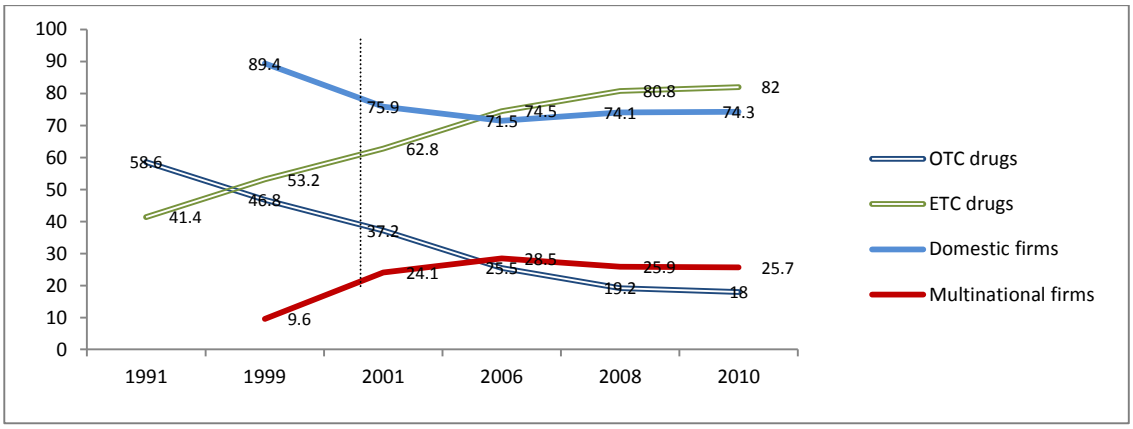

Figure 4.6: The change in the pharmaceutical market after SPD in 2000

Source: KHIDI (2010b), HIRA Statistics

(a) First, the increasing demand for ETC drugs became a considerable threat to most domestic firms, as their product portfolios were mainly based on OTC drugs and (off-patented) generic drugs. Physicians generally prefer original branded drugs to generic drugs. The sharp increase in ETC drugs was partly due to the direct effects of the SPD.[98] Prior to the reinforcement of the SPD, many patients had a tendency to go to chemists when they felt that their diseases could be managed by drugs alone, without seeking a diagnosis from a physician. However, the prohibition of arbitrary prescription by chemists resulted in an increase of ETC drugs prescribed by physicians.

(b) The other notable change was the direct encroachment on the market by Big Pharma with innovative ETC drugs rather than giving licenses to domestic firms. The direct intrusion of Big Pharma was based on the changing pricing system for drugs and the inclusion of imported drugs on the drug reimbursement list after the reform, which made importing new drugs more favourable. Subsequently, Big Pharma companies rapidly increased their market share after the reform of the NHI around 2000 (Figure 4.6).

As a consequence, the changing market selection environment led to a narrowing of the market leadership of domestic firms.

4.4.3 Intermediate outcome of the change

[98] The other reason is the increasing chronic diseases, such as lifestyle diseases as income levels become higher, and as a consequence of aging in society.

In response to these changes, two opposing movements by domestic companies can be identified: i) a rush into the generic ETC drugs to supplement the sharp decrease of OTC drug sales,[99] and ii) reinforcement of new-drug development.

i) For most domestic companies, the production of generic drugs became a survival strategy to compensate for a lack of innovative capability. This was in large part because of the government's supportive position for generic drugs. By 2006, the pharmaceutical reimbursement policy had maintained an apparently high reimbursement rate for the first-listed generic drugs, up to 87% of the original drug price. As a result, domestic companies were able to enjoy, to some extent, very lucrative revenues from maintaining their generic drug business, just as they did in the 1990s.

ii) Some domestic companies reinvested the profits acquired from the higher pricing of generic drugs into new-drug R&D. IMDs, NCEs, and biological drugs developed through exploratory learning have begun to emerge in the domestic market and R&D pipelines over the past decade. In 2008, one phytomedicine and one IMD developed by domestic companies (Stillen by Dong-a and Amodipin by Hanmi) were on the top ten sales list for outpatient prescriptions (Table 4.4). On the top 100 list, there was one NCE (Revanex by Yuhan) and three more IMDs. Furthermore, a domestic company, LG Life Science, acquired an NDA from the US FDA in 2003 for its new drug, Factive.

Table 4.4: Top 10 ETC drugs and firms (outpatient prescription sales)[100]

Rank	Item (in 2008)	Launching company (Original developer)	Size of EDI-based claim (Unit: Korea billion won)
1	Plavix	Handok *(*Sanofi-Aventis*)*	111.1
2	Novask	Pfizer	75.3
3	Lipitor	Pfizer	70.7
4	Stillen	Dong-a	69.3
5	Gleevec	Novartis	677
6	Amodipin	Hanmi	55.9
7	Ultra	Bayer	47.3
8	Crestor	Astra Zeneca	44.2
9	Olmetec	Daewoong (Daiichi Sankyo)	44.0
10	Gasmotine	Daewoong (Eisai)	415

Source: Edit from Yakup Newspaper Statistics 2010, EDI: Electronic Data Interchange

[99] Product patents of 183 new drugs (branded drugs) expired between 2008 and 2013.
[100] The size of the EDI (Electronic Data Interchange) based claims (bills) represents the sales size of outpatient prescription drugs, reflecting the real marketing performance of pharmaceutical companies under SPD.

To some degree, this indicates real achievements in domestic pharmaceutical companies' transition to being new-drug developers. This initial performance is the outcome of long-term trials in new-drug development spanning 20 years. On the other hand, it should be noted that there is still a great deal of failure and stagnation of new-drug R&D.

In summary, the appearance of new drugs on the domestic market is the intermediate outcome of new-drug R&D initiated by the enforcement of the product patent system in 1987, and its acceleration by the reform of the NHI in 2000. Although market competition based on generic drugs is still the major criterion for market survival, the new market selection criteria based on new-drug R&D have been increasingly influencing the survival and growth of domestic pharmaceutical firms. Further, institutional measures to prevent informal marketing activities for selling generic drugs and FTAs with the US and the EU started in the 2010s, accelerating the changes in the KoPI's market selection environment.[101]

4.5 Changing S&T Policy Landscape

While the changes in the patent system and NHI, and the resulting alterations in the market structure, have forced domestic companies to conduct R&D for new drugs, S&T policies (and partly industrial policies) have directly influenced the endogenous pattern of new-drug R&D. Three policy changes particularly affected new-drug R&D.

First, the incumbent pharmaceutical industry conducted new-drug R&D under an overall lack of industrial policy during a considerable part of the transition period, until its recent reappearance (Sub-section 4.5.1). In contrast, emerging biotechnology has been strongly supported by a series of industrial and S&T policies from its conception (Sub-section 4.5.2). Finally, S&T policies are universally changed, particularly in managing R&D programmes to promote the generation of innovation (Sub-section 4.5.3).

4.5.1 Disappearance and reappearance of industrial policies

While imitative capability in the KoPI was successfully accumulated under the strong industrial policy for import substitution of APIs by the early 1980s, no further industry-

[101] To eradicate such marketing patterns based on illegal rebates aimed at lowering the actual transaction price system, in 2010 the government introduced a so-called 'dual punishment system' between physicians and pharmaceutical companies. This punishment system caused additional turmoil among the stakeholders of the pharmaceutical companies, physicians and chemists, thereby influencing the market performance of the companies, under the policy change of generic drug pricing in the late 2000s.

specific industrial policies were actuated in the following transitional period under the liberalisation of the commodity and capital markets.[102]

In the absence of industrial policies for an industrial upgrade, the product patent regime and the reformed NHI operated as practical institutional signals to determine domestic firms' marketing and technological activities. Given the industrial policy vacuum, as will be seen, pharmaceutical firms' new-drug R&D has been supported only in fragmented fashion, to a large extent under the policy to foster emerging biotechnology rather than any sector-specific policy.

However, in 2011, a pharmaceutical-sector-specific industrial policy was instituted, aiming to provide comprehensive support to the industry, including the promotion of new-drug R&D, commercialisation and export.[103] Interestingly, the pharmaceutical industry-specific industrial policy overlaps with national policies for supporting emerging biotechnology due to similarities in the two industries' knowledge base and target market.

Overall, the period of the most transition in the KoPI proceeded without any comprehensive industrial policy until recently.

4.5.2 National attention to biotechnology

The Korean government has been attracted by emerging biotechnology as the prominent momentum of the next generation of economic development since the 1990s. Since then, despite the stagnated growth of biotechnology as an industry, a series of S&T policy measures, including large-scale R&D investment, were carried out to establish infrastructures and a knowledge base for biotechnology. In a sense, the active S&T-policies to support biotechnology, instead of relying on industrial policies, can be seen as an effective substitute for the Industry-specific industrial policy because of the deep reliance on scientific research of the industrialisation of biotechnology including drug R&D.

Specifically, the Promotion Act for Genetic Engineering drew public attention to biotechnology, igniting the first boom of biotechnology between the mid- and late-1980s (Table 4.5). On the basis of this Act, the Genetic Research Centre (GRC) was established under the Korean Institute of Science and Technology (KIST) in 1985, led

[102] In the Korean catch-up context, the industry-specific industrial policies for each industry served as a kind of guidepost for the subsequent supportive policies such as the financial and R&D support, procurement and export support (Heo 2001).
[103] The Pharmaceutical Promotion Act was intended to cope with the threat of FTAs with the EU and the US.

by the Ministry of Science and Technology (MOST). It was expanded as the independent GRI, Korea Research Institute of Bioscience and Biotechnology (KRIBB). The Ministry of Trade, Industry and Energy (MOTIE) also began to support the industrialisation of biotechnology. The Biotechnology Association of Korea, composed of DBFs, was founded as a leading industrial community approved by MOTIE in 1991.

Table 4.5: Key S&T policies for the development of the biotechnology

Year	Industrial and S&T policies (leading ministry)	Policy implementation
1983	Promotion Act for Genetic Engineering (MOST)	- Genetic Research Centre - Korea Genetic Engineering Research Association
1989	Plan for the Development of the Biotechnology Industry (MOTIE)	- Biotechnology Association of Korea
1994	Promotion Act for Biotechnology (MOST)	- Korea Research Institute of Bioscience and Biotechnology
1994	: First Promotion Act for Biotechnology (MOST) - *Biotech 2000*	- Long-term, large-scale NRDPs : Frontier Programme
2007	: Second Promotion Act for Biotechnology (MOST) - *Biovision 2016*	- Enlargement of the Frontier Programme - Focus on industrialisation of biotechnology

Source: Author's elaboration based on several policy reports

In 1994, as the most fundamental and comprehensive S&T policy, the Promotion Act for Biotechnology, called *Biotech 2000*, was established in an attempt to comprehensively support the emerging technological field and to clarify the role of relevant ministries in fostering the biotechnology industry, such as MOST, MOTIE and the Ministry of Health and Welfare (MOHW) (National Archive 2007).[104] The new plan, mainly designed by MOST, largely focused on three perspectives of the innovation system: the necessary establishment innovation actors; a detailed plan for the execution and coordination of R&D policies, and the accumulation of human resources in biotechnology (*ibid*).

Through the Biotech 2000 project, Korea was estimated to have established an innovation system of biotechnology facilitating R&D capabilities of the participants and R&D collaboration between the private and public institutes (Chung 2001).

This act has been continuously amended, stressing the industrialisation of biotechnology over the last decade. In line with this, the government published the Second Framework Plan for the Promotion of Biotechnology, the so-called *Bio-vision 2016*, which started in

[104] The first stage was to arrange the supportive policies for R&D activities, while the second stage focused on producing the outcomes of R&D. The third stage was meant to commercialise the scientific products.

2007. This act aims to regain status as a G7 country and strengthens the funding size by three times more than the first promotion act (about US$14 billion by 2016).

Table 4.6: Main NRDPs related to drug R&D

National R&D programme	Number of firms	Period	Executive ministry
Special R&D programme (firm-led R&D)	17	1987 ~1989	MOST
Special R&D programme (government-led)	22	1990 ~ 1992	MOST
HAN Project (G7 Project)	26	1992 ~ 1997	MOST
Intermediate Core Technology Development	9	1993 ~ 1994	MOST
Core Industry Technology Development	17	1994 ~ 1996	MOST
Core National R&D Project	6	1998 ~ 2002	MOST
Bio-Challenger Project	2	2003 ~ 2005	MOST
Biomaterial Development Project	1	2003 ~ 2004	MOST
Health and Medical Technology Development	36	1996 ~ present	MOHW
Midterm Technology Development	13	1998 ~ 2002	MOTIE
Strategic Technology Project	16	2005 ~ present	MOTIE
Bio-Star Project	8	2005 ~ present	MOTIE

Source: Revision based on KDRA Whitepaper (2009)

Under the policy acts, the series of NRDPs to promote biotechnology R&D have increasingly been launched, including the Highly Advanced National (HAN) programme, Science Research Centre (SRC), and Engineering Research Centre (ERC) projects (Table 4.6).[105]

The first R&D programme was initiated in 1987 by MOST in response to the enaction of the product patent system in 1987. It was further supported under the HAN programme (i.e., the so-called G7 project) to develop frontier technologies.[106] MOHW also started to support new-drug R&D through Health and Medical Technology Development, starting in 1996. Overall, the number of NRDPs and the size of R&D expenditures have increased

[105] Biotechnology-related projects accounted for about 25% of all SRC and ERC projects by 1999, aimed at building the upstream research capability of universities. The nine-year long R&D project of SRC and ERC was launched on the basis of the Promotion Act for the Advancement of Basic Science Research enacted in 1989, to raise the excellence of basic research groups (SRC) and goal-oriented applied research capability with a view to its industrial exploitation (ERC). The SRC and ERC were one of the representative national R&D projects of the 1990s, broadening the scope of knowledge bases and funding size. The Promotion Act contained fourteen biotechnology-related projects, such as biomedical engineering.

[106] It is often referred to as the G7 project, implying the ambitious goal to raise the technology level to that of the advanced G7 countries, especially in engineering and technology fields such as semiconductors, high definition TV (HDTV), nuclear energy and mechanical areas. One of eighteen projects was to develop new drugs between 1992 and 1997.

almost proportionately since 1993, especially after the recovery from the Asian economic crisis in the late 1990s (Figure 4.7).

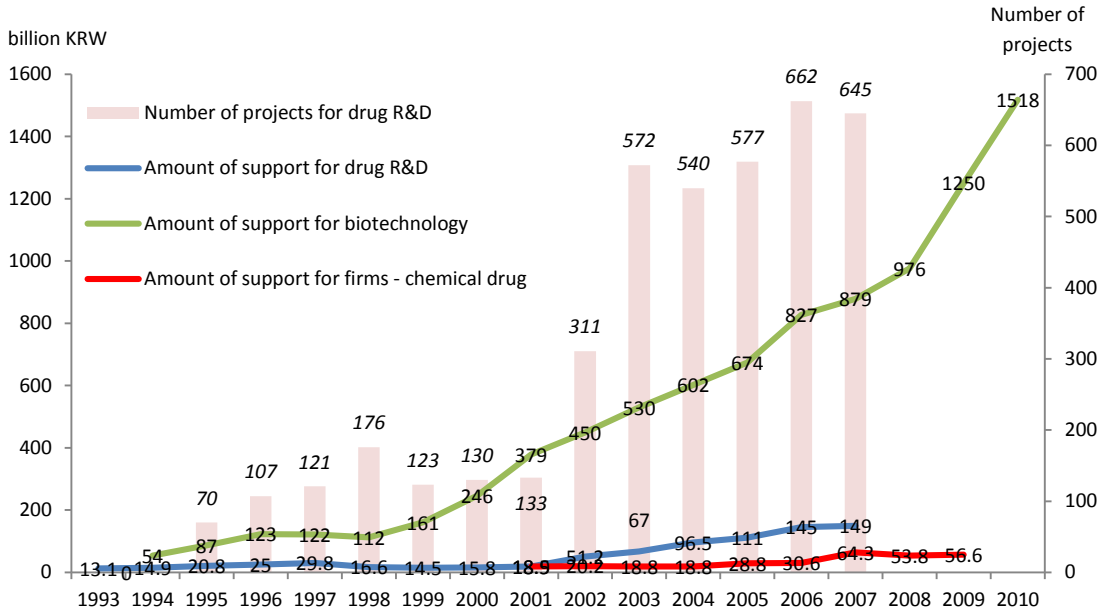

Figure 4.7 Government Investment in drug R&D

Source: Data from KHIDI reports (2002, 2005, 2010b) and the KHIDI White Paper 2009 (2010b)

To sum up, all subsequent biotechnology-related NRDPs based on the Biotechnology Promotion Act, Biotech 2000 and Biovision 2016 show Korea's desire to take biotechnology leadership beyond the imitation stage of existing technologies. Indeed, Korea has boldly increased R&D investment in biotechnology compared with other technologically advanced countries (Table 4.7)

Table 4.7: Public R&D spending on biotechnology

Country	2003		2009	
	Million PPP $	As % of total public R&D spending	Million PPP $	As % of total public R&D spending
Canada	550	12	724	7
Denmark	131	10	199	10
Finland	105	7	129	5
Germany	-.	-	4,605	21
Korea	727	15	2,083	20
Singapore (2005)	360	28	-	-
Spain	452	-	1,302	14
Taiwan	618	31	-	-
United Kingdom	212	2	-	-

* Public spending: Government and higher education, PPP: Purchasing power parity

Sources: OECD Biotechnology Statistics Database (2011) and Wong (2011)

In addition, the active national investment to biotechnology is also identified in the rapid increase of the industrial researcher in biotechnology-based R&D including the pharmaceutical sector, as an outcome of national education (Figure 4.8).[107] At the same time, it should also be noted that 70% of PhD researchers are estimated to belong to public R&D organisations such as universities and GRIs (Kim 2004). In the more specific context of drug R&D, for example, three GRIs, KRIBB, KIST, and Korea Research Institute of Chemical Technology (KRICT), were operating 474 researchers, including 160 PhD researchers, with about US$50 million, mostly focusing on drug discovery research in 2004 (*ibid.*). It can be thought of as a considerably affluent R&D environment compared with the then total number of PhD researchers, 1,102, in an industry containing 640 companies.

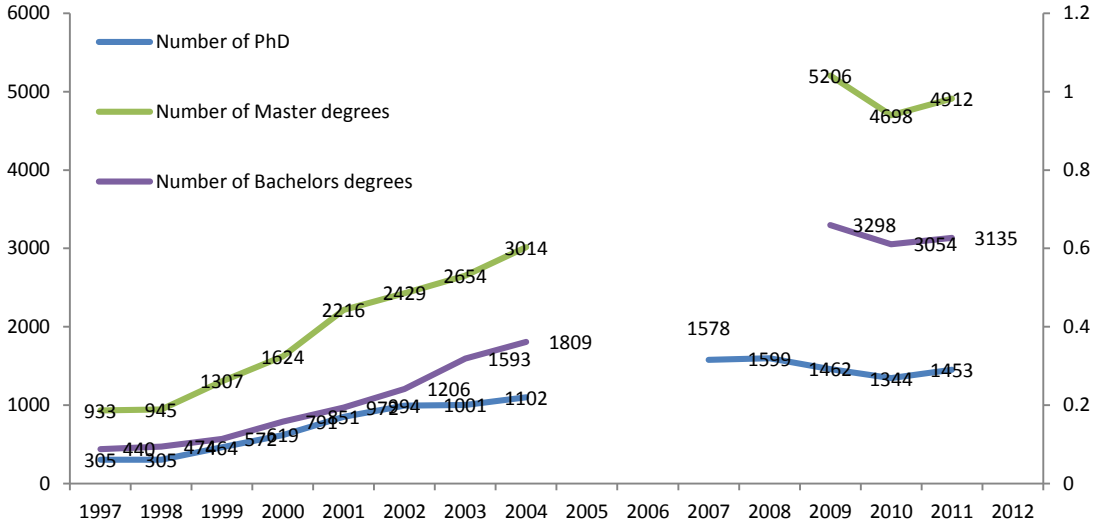

Figure 4.8: Number of industrial researchers with PhD, master and bachelor degrees

Source: Data from KHIDI (2006a) and MOTIE and KoreaBio Survey report (2014)

4.5.3 Changes in detailed S&T policies for R&D support

S&T policies, which directly influence the R&D patterns of innovation actors, have been reformed to promote innovative learning since the 1990s, i.e., explorative technological learning. The main changes have been fully reflected in the design and conduct of NRDPs. Specifically, incentive and evaluation structures for researchers in the public sector (GRIs and universities) have been rearranged from the stable allocation of R&D funds from the government to the performance-centred competition system, the so-called project-based system (PBS). However, S&T policies have long been dominated

[107] No data were available for the years 2005, 2006, and 2007 in Figure 4.8.

by civil service and professionals from the public sector (Song 2006) and reflect the selection environment of NRDPs. Administrative leadership of R&D support in biotechnology, including new-drug R&D, has rapidly diversified from MOST to MOHW and MOTIE. The multi-level change in S&T policies will be discussed as the main object of the analysis in the following chapter.

4.6 Summary

This chapter addressed the major institutional and technological pressures in the global and local contexts, and the resulting changes in the market selection environment that initiated and accelerated new-drug R&D in the KoPI. In addition, it presented the macro-level changes in S&T policies that have directly affected the technological learning pattern of innovation actors in the transitional phase.

First, the new-drug R&D process was presented. The illustration of the new-drug R&D process showed technological, institutional and financial barriers to entry into the new-drug business by the latecomer firms. It also pointed out the decreasing productivity of new-drug R&D by Big Pharma and the increasing generic drug market. The changing industrial context has provided local latecomer firms with new opportunities for catch-up, regardless of whether they have taken on these opportunities in reality.

Second, in the local context, this chapter illustrated the rapid change in the domestic institutional context, the introduction of the product patent system and the strengthening NHI, and thus the change in the market competition environment toward a technologically intensive ETC drug market (away from intensive marketing of OTC drugs). In response to the change, the domestic latecomer firms that were able to accumulate production capability by following reverse PLC have tried to transition from generic drug producers into new drug developers. The development of a few commercially successful new drugs (NCEs and IMDs) signals that the KoPI has been engaging in this transition.

This chapter also showed that the increasing new-drug R&D has been implemented under the macro level S&T policy changes. The government has increasingly supported the emerging biotechnology, which is the major innovation source for new-drug development. It also presented that the general S&T policies for R&D support have also been changed towards innovation creation.

Overall, this chapter clarified the general new-drug R&D activities and diverse institutional factors influencing the transition of the KoPI. However, while the causes (the product patent system and NHI) and intermediate outcomes (a few commercial

successes among about 20 new drugs developed) of the transition have been identified, the transitional process through new-drug R&D under the change of S&T policies remains unknown. The following three chapters address the transitional process.

Chapter 5: The rearranged S&T policies and Exploratory learning

> "It was the biotechnology that the last five presidential governments, from president Roh Tae-woo (1988-1993) to Lee Myung-bak (2008-2013), continuously declared as the economic growth engine. However, what is the result of the enormous financial input? Far from being a core industry of the country, it lags behind Thailand. Total sales size of the Korean pharmaceutical companies does not reach even top 20th company in the global pharmaceutical industry" (Dr Chang-ho, Ahn, a CEO of Rexahn Pharmaceuticals in the US, Korea Economic Daily, 3/5/2013).

5.1 Introduction

Chapter 3 (Sub-section 3.3.2) discussed the institutional promotion of exploratory learning in terms of changes in the three policy dimensions surrounding national R&D programmes (NRDPs): R&D investment, an incentive regime and a ministerial pattern of administrating NRDPs.[108]

By analysing the three policy dimensions surrounding new-drug-related NRDPs, this chapter uncovers the influence of reformed S&T policies on innovation actors' exploratory learning. The analysis is mainly based on interviews with researchers from the three Frontier programmes, and complementary interviews with representatives of industrial associations, domestic pharmaceutical companies, DBFs and Big Pharma.

Section 5.2 presents the overall increases in R&D investment in new-drug R&D and the increasing problems with R&D investment. Section 5.3 describes the incentive regime of NRDPs and their problematic influence on innovation actors' R&D activities. Section 5.4 identifies the administration pattern of the three leading ministries in supporting new-drug R&D and industrialisation. Section 5.5 presents the negative effects of the policy implementation on exploratory learning. Section 5.6 summarises the chapter.

5.2 R&D Investment for New-drug R&D

This section analyses the rapid development of NRDPs, which have been aimed at promoting new-drug R&D over the last 25 years. NRDPs are designed by government ministries on the basis of S&T policies. Both public and private innovation actors are

[108] As noted, NRDPs were treated as the institutional interface that links S&T policies and innovation actors' technological learning (Chapter 3, Sub-section 3.4.1).

beneficiaries of NRDPs as project leading organisations, main contractors or sub-contractors.

The positive effect of NRDPs on promoting exploratory learning is analysed in Sub-section 5.2.1. By contrast, the second sub-section (5.2.2) discusses the increasing imbalance between the supply and demand sides of NRDPs, particularly in the past 10 years.

5.2.1 Positive effects on the promotion of new-drug R&D

The rapid increase in government R&D investment in biotechnology, including new-drug R&D, has already been presented (Chapter 4, Sub-section 4.5.2). NRDPs have generally been structured as widely distributed small projects. For example, in 2007, government funding for drug R&D was allocated to 556 projects, each of which received an average of only KRW 331 million (about US$ 0.3 million) (Table 5.1). Essentially, government R&D funding has operated as a kind of 'seed money', although the amount of R&D funding per project has gradually increased (Interviews 19, 33 and 41). Despite this relatively small and fragmented R&D support, a few positive outcomes from R&D can be identified, particularly in the first round of innovative R&D in the 1990s.

Table 5.1: Government drug R&D investment classified by actors in 2007

Types of actors		Number of projects	Amount of funding	Funding per project
Public actors	Universities	391 (60.6%)	63,100 (42.5%)	161
	GRIs	76 (11.8%)	29,500 (19.8%)	388
Pharmaceutical firms		89 (13.8%)	39,800 (26.6%)	445
Total[109]		556 (86.2%)	132,400 (95.7%)	331

* Unit: Millions of KRW
Source: Recalculation based on the data from KHIDI Survey reports (2005, 2006a, 2008)

First, the public primary actors, namely universities and GRIs, consolidated their research base by becoming the largest beneficiaries of the drug R&D projects. The role of these public actors in establishing a knowledge base for upstream biotechnology and downstream drug development was praised by the pharmaceutical industry (Interviews 6, 9, 18 and 20 (DBF); 45 and 51 (K-Pharma)). For example, the scientific performance

[109] The rest of these include government departments and other types of public actors.

of the Korean biotechnology sector rapidly increased, according to the number of papers in the SCIE (Science Citation Index Expanded), which placed Korea 11th in the world rankings in 2010, up from 29th in 1994 (Figure 5.1). The number of patents applied also increased in the last decade (Figures 5.1 and 5.2).

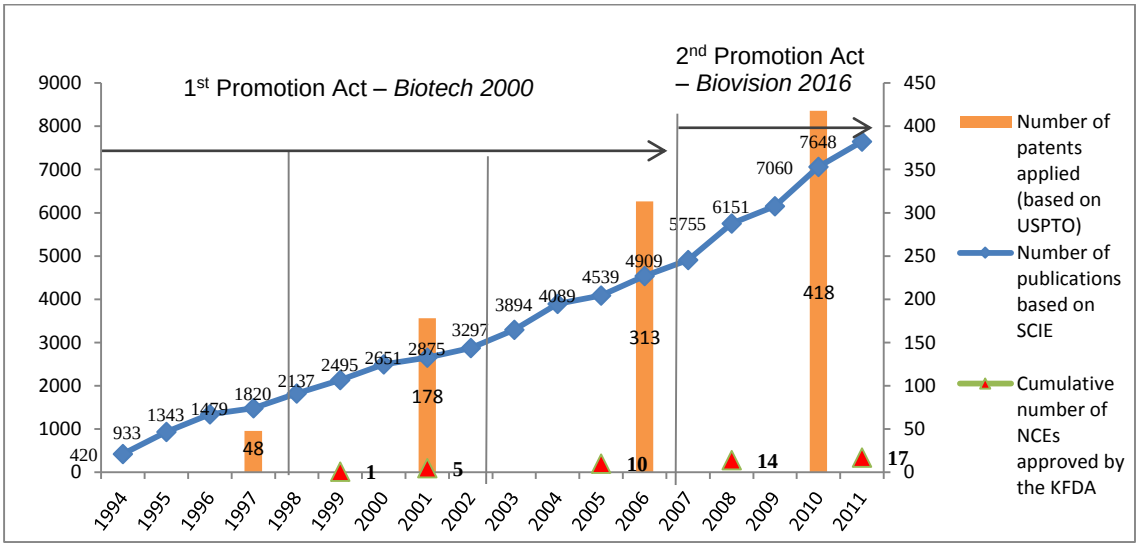

Figure 5.1: The performance of biotechnology R&D in the transitional period

Source: data from Biovision 2016 and KDRA white papers

Second, for the pharmaceutical firms, although the NRDPs allocated to the pharmaceutical industry were relatively tiny and scattered (Table 5.1), such support was critical because it acted as a policy-induced promoter of the entry of domestic firms into highly uncertain technological exploration and new-drug development (Interviews 42, 44, 48 and 51 (K-Pharma)). The pharmaceutical firms were able to accumulate basic experience in new-drug research (e.g., drug identification) and engage in collaborative R&D with GRIs and universities (KDRA 2005). All 15 NCEs domestically approved by KFDA were partially supported by NRDPs in the 1990s and the 2000s, accounting for 7.97% of the total R&D investment for the 15 drugs (KDRA 2009).

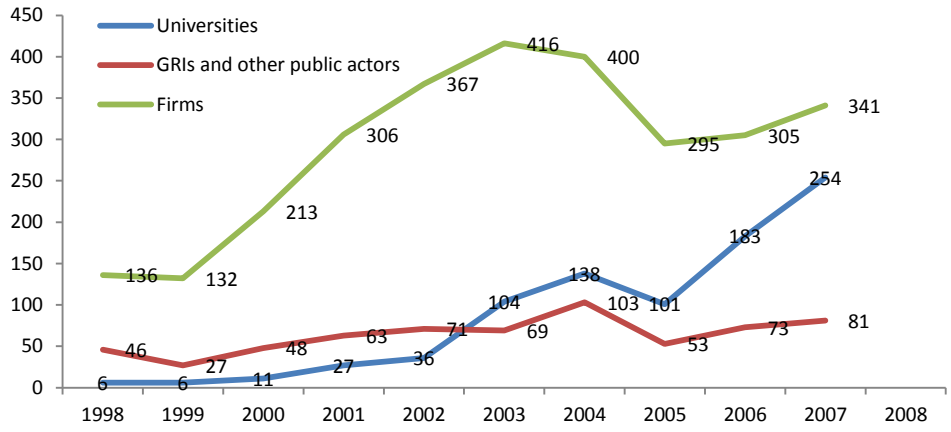

Figure 5.2: Patent performance of innovation actors in drug R&D

Source: Recalculation based on the data from KHIDI Survey reports (2006a, 2009)

5.2.2 The mismatch between R&D investment and demand

However, the small proportion of national R&D support for pharmaceutical firms has become one of the key grounds upon which industrial actors have criticised the effectiveness of NRDPs for drug R&D.

In 2009, national R&D support accounted for just 10.7% of pharmaceutical firms' drug R&D budgets, while self-funding accounted for 88.8% of total R&D expenditures (data from KHIDI 2010a). Moreover, for a total of 68 new drugs developed, including NCEs, IMDs, and biobetters/similars, government R&D funding accounted for just 7.1% of total R&D expenditure, according to the KHIDI Survey (2012). In this respect, it is difficult to ascertain whether firms' rapid increase in patenting in the 2000s, and their advances in new-drug development, were really driven by the government's R&D support.

The recent discontent with national R&D support is mainly attributable to the increasing burden of new-drug R&D with only the slightest change in the support pattern of the NRDPs, which remain public-oriented and fragmented.[110] There have been two changing needs for R&D support: a) an increasing demand for larger-scale NRDPs for clinical development, and b) an increasing demand for external sources of drug candidates.[111]

a) Industry actors are seeking more large-scale support at the development stage, such as support for clinical trials, especially for the first and the second stages (Interviews 40, 46, 49 and 51 (K-Pharma), and 9, 19, 33 and 36 (DBF)). R&D support

[110] The dissatisfaction with the NRDPs from the DBFs was also identified in the interviews, often with criticism of the behavioural pattern of pharmaceutical firms. This will be further explored in later sections.
[111] Five of the seven interviewed (from leading pharmaceutical companies and two DBFs that are now operating their own clinical development projects) pointed out the difficulty of conducting clinical trials by internal R&D investment alone: CKD, Dong-a, Hanmi, Yuhan, and Crystal Genomics and Viromed.

for clinical development was actually implemented primarily by the MOHW in the Health Technology Programme, but in the form of seed money. They claim that drug development itself intrinsically means a central role for private firms' commercialising activities. Without the pharmaceutical firms, upstream research by the public and DBFs cannot bear the real fruit of commercially viable new drugs. Therefore, government support should strike a greater balance between upstream research support and downstream development support.

b) The other demand has been directed towards a more effective institutional mechanism for collaborative research in deriving drug candidates (Interviews 39, 49, 52 and 53 (K-Pharma)). This comes from a critique of R&D collaboration with public actors, particularly universities, through NRDPs. Pharmaceutical firms have increasingly demanded external sources that can supply potential drug candidates to complement their internal weakness in the upstream discovery research. While private sector interviewees admitted the importance of supporting public upstream research, they questioned the commercial viability of the candidate materials developed by universities and GRIs.

KDRA data indicates that such changing demand is broadly applicable among domestic firms conducting new-drug R&D. In total, 42.9% of 35 responding firms (out of 55 member firms of KDRA) chose the development stage (preclinical and clinical stages) as the highest priority for government support; 20.8% stated that the second highest need was effective support to outsource drug candidates (KDRA 2009).

Overall, entering the 2000s, the demand of pharmaceutical firms for R&D support has noticeably intensified and been diversified, ranging from upstream research to the clinical development stages. In contrast, the pattern of NRDP fund distribution has hardly changed, concentrating on supporting upstream public research with seed money and paying attention to emerging biotechnology. This has resulted in an increasing mismatch between the on-going supply pattern and the changing needs of national R&D funds, although the scale and scope of drug R&D support has increased.

5.3 Incentive Regime of National R&D Programmes

This section discusses the NRDP incentive regime, which consists of evaluation mechanisms, represented by the project-based system (PBS), and professor-led selection of R&D projects, expressed as a closed policy network. Ultimately, this section

will trace how the incentive regime has, in effect, caused system-wide problems in promoting an exploratory mode of technological learning.

The micro-level evaluation mechanism under PBS shows an increasing contradiction between the incentive structure for researchers and the goal of NRDPs to promote innovation (Sub-section 5.3.1). The NRDP selection environment exhibits an institutional lack of linking public and industrial R&D activities (Sub-section 5.3.2).

5.3.1 Evaluation pattern of national R&D programmes

5.3.1.1 Project-based incentive structure

The allocation system of national R&D funds, which determines the incentive structure of beneficiary organisations and researchers, changed to the PBS in 1996. This new system was introduced to promote innovation by broadening the autonomy and strengthening the transparency of conducting R&D projects (Lee 2006).

Prior to the introduction of the PBS, government R&D funds were stably supplied by top-down, mission-oriented NRDPs (Lim 2000). Little competition among research groups and organisations was needed (Interview 13 (GRI)). Thus, NRDPs were able to be stably conducted by a team or department base comprising 10-20 researchers led by a team leader (Kim 2011). These mission-oriented NRDPs were effective in the catching-up stage at localising foreign technologies and products under a clear industrial policy (Suh 2000). However, on the negative side, team leader-centred project allocation and operation caused bureaucratic and unclear management of NRDPs (*ibid.*). The PBS was introduced to solve such problems and encourage innovative research.

Since the introduction of the PBS in 1996, research projects have been acquired by competition between research teams. The PBS operates via a quantity-based evaluation of research performance known as 3P; it looks at the number of publications, patents, and projects obtained (and the return of technology transfer). Under the PBS, competition to obtain R&D projects has been considerably intensified to supplement researchers' salaries, which are set at a base level (Interviews 4, 13 and 28 (GRI)).

5.3.1.2 Dual effects of the project-based system

Amid competition to acquire research projects, and due to its stress on quantity-based performance, the PBS has had dual effects on the operation of NRDPs. As noted, on the positive side, a significant improvement in research performance, especially in terms of knowledge accumulation in the form of papers and patents, was identified (Figures 5.1 and 5.2).

However, on the negative side, industrial potential became a secondary concern after publication and 'blinding' patenting (regardless of any real application or technology transfer). That is, the PBS forced researchers to prioritise quantitative performance based on publication and patenting (Lee 2003, Yim and Kim 2005) to secure the continuation of projects, which are normally evaluated every year (Interviews 11, 13, 26 and 27 (GRI)).[112]

Moreover, increased competition has caused inevitable overlap of research topics between R&D teams in a few trendy and popular areas such as 'bio nano-', 'bio-drug', or 'stem cell'. This tends to minimise the risk of selection failure when applying for NRDPs by benchmarking others' research topics (Interviews 11 and 26 (GRI)).

A team leader of a drug research project at a GRI, the Korea Research Institute of Bioscience and Biotechnology (KRIBB), characterised these negative effects as an overall outcome of the new incentive system (Interview 26):

> We [team leaders who were responsible for acquiring projects] could not put innovation and commercial potential first when we applied for a project, though we recognise the importance of industrial potentiality in national projects based on people's tax. For us, guaranteeing the continuation of present projects and acquiring more projects are the most critical tasks for maintaining our research team and keeping our team members' salary at a certain level.[113] Because of this, a considerable part of our time at work is spent not conducting research, but applying for projects, networking with administrative officers and reporting the interim and final results every year.[114]
>
> Under the PBS, no researchers would be willing to conduct explorative long-term research. A failure in obtaining a successful research outcome means subsequent failure of acquiring the next NRDP. Thus, many projects implicitly attempt to benchmark other research projects to avoid the risk of failure. Thus, research topics become similar, focusing on a few popular research areas.[115]

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[112] Specifically, they pointed out PBS as the most serious inhibitor that disturbed the long-term, more exploratory research in GRIs, even within a long-term project, due to annual and quantity-based interim evaluations.

[113] 'Besides, we [researchers] actually can perform a few research projects but we propose many projects by packaging them like different topics. Although we know it is wrong, we have to first concern ourselves with the evaluation based on the PBS. We make different project reports with a few original projects.'

[114] In reality, in a survey of the PBS to researchers in GRIs and universities, conducted by a member of the National Assembly, Doo-un Chung in 2011, 43% of the total number of respondents indicated private networks as the most important factor to acquire NRDPs (the total number of respondents – 345).

[115] This was also pointed out by a team leader of the KIST, Dr Ji-yun, Kang (Interview 11).

In fact, in 2010, 95% of all NRDPs resulted in the successful completion of their projects, according to the National Science and Technology Commission (NSTC). According to Dr Chang-gyu Hwang, former head of R&D strategy at MOTIE, this means that there was almost no risk-taking R&D. 'R&D fund was given to projects that were almost guaranteed success', he said. That is, R&D funds were used for technological validation in repetition rather than exploration.

The prioritisation of quantitative criteria based on publication and blind patenting prevails not only at GRIs, but also at universities. An assistant professor in a biotechnology department at a university who succeeded in transferring a research outcome to a *Chaebol* (SKC) criticised the fact that the benchmark in evaluating promotion is the quantity of publications. Technology transfer is not regarded as being as valuable as publications, even though most of the university's royalties are obtained through technology transfer (Interview 22 (university)).[116]

Publication-centred evaluation has also influenced private innovation actors' participation in NRDPs, particularly that of DBFs. The former president of the Korea Biomedicine Industry Association (KOBIA) pointed out that the government also based the distribution of R&D funds to industrial developers such as DBFs on publications (Interview 20 (DBF)).[117] It is inevitable that DBFs will prioritise publication in order to acquire NRDPs.

The negative effects of this quantitative, performance-oriented incentive structure are amplified by the low impact of scientific publication done in Korea. Korea had the lowest impact factor among OECD countries while producing the 11th highest number of publications (based on SCI), according to a survey conducted by NSTC in 2011 (The Hankyoreh, 14/2/2012).

Related to this, a leading researcher at the Korea Institute of Machinery and Materials (KIMM) pointed out that integrative R&D planning that reflects commercial potential and demand is difficult to set up if each team or researcher is making dispersed and competitive project applications. Under the present structure of the PBS, research results with high commercial potential will not be produced (Daedeok Net, 11/8/2011).

Summarising remarks

[116] Technology transfer about micro-needle technology in 2007.
[117] The CEO of Proteogen and the former head of Genetic research centre (GRC, the forerunner of KRIBB) of KIST.

Overall, this sub-section traced the problematic aspects of the PBS-based incentive structure. Innovation performance of NRDPs has been mainly expressed in the rapid accumulation of publications and patents, making the NRDPs appear successful for the science-driven transition. However, while a good quantitative performance in the short term means the 'administrative' success of NRDPs and guarantees the sequential acquisition of new research projects, it does not always lead to the establishment of promising research activities and successful industrial development. That is, it is difficult to ascertain whether PBS has promoted autonomous, long-term, risk-taking and industry-reflective research.[118]

5.3.2 Selection mechanism of national R&D programmes

5.3.2.1 Professor-led selection environment

This sub-section investigates the selection mechanism for research teams and research projects.

The most noticeable characteristic of this selection mechanism is the over-dominance of professionals from academia and GRIs and their close relationship with the civil service, which has administrative power of the allocation of R&D funds.[119] Together they formed a 'closed policy network' when the NRDPs were planned and selected in a top-down style in the catching-up era (Song 2006). Participation in this network was one of the most important criteria for receiving national R&D funds (*ibid.*).

In the imitation stage, planning and selection of NRDPs was relatively simple. As the targeted industries and technological fields were already present in the advanced countries, the closed policy network was relatively effective for R&D support (Song 2006), due to the lower level of technological uncertainty and institutional complexity in the imitation stage. That is, the technological goal of the NRDPs and learning path was clear.

In contrast, at the beginning of the transitional phase, the complexity surrounding technologies and industrial upgrading exceeds the administrative ability of policy makers. Moreover, stakeholders related to innovation activities have also increased; they include expanding universities and incumbent firms as well as new technology-based start-ups. Notwithstanding the changing environment, this institutional custom still seems to be prevalent in the present NRDP selection process for new drugs and biotechnology.

[118] A summary of comments on PBS is given in Appendix 5.
[119] The civil service assumed the top position in the social hierarchy (Kim 2001a).

More specifically, the closed policy network has continued in the interdependence between the civil service and professionals from universities and GRIs. Basically, the civil servants in charge of designing S&T policy lack knowledge of S&T (Kwon et al. 2002, Park 2008), because civil service personnel are generally promoted for their administrative abilities (Park 2008). Thus, policy makers have increasingly relied on these professionals, creating a closed policy network (Park et al. 2005, Song 2006), although the government has recently tried to better reflect the industrial voice by expanding the participation of industrial professionals in the process of planning S&T policy and selecting NRDPs.

Table 5.2: Distribution of committee members in the NSTC by affiliated fields

Period (Year)	Academia	GRIs	Civil Service	Industry	Others
1 (1991)	6	1	3	1	2
2	3	4	4	1	1
3	6	3	4	2	0
4-1	4	4	2	1	0
4-2	5	4	1	0	1
5	7	3	1	2	1
6	4	3	1	2	1
7 (2005)	3	3	1	2	1
8	11	5	2	7	5
Total	49	30	19	18	12

* NSTC: National Science and Technology Commission
* *Source*: Park et al. (2005)

For example, Tables 5.2 shows the overall dominance of academia (and GRIs) in the macro-level commission (National Science and Technology Commission; NSTC) led by the president. Between the first and seventh periods (from 1991 to 2005), there were very few members from industry on the commission. Table 5.3 also presents the prevailing distribution of committee members from universities in the real selection level of NRDPs, here, the Health Technology Programme.

Table 5.3: Distribution of committee members on the HT Programme in 2006

	Universities	GRIs	Industry	Civil service
Number of members	12 (from 7 universities)	3	3	2

* *HT Programme: Health Technology Programme*
* *Source*: Recalculation from the data of KHIDI (KHIDI 2006b)

5.3.2.2 Problems of the closed policy network

Related to this, an interviewee who has worked in both the civil service (1996 to 2006) and Big Pharma (2007 to present), discussed some of the negative effects of the civil service- and professor-led policy network in the institutionalising process of new-drug and biotechnology NRDPs and industrial promotion as follows (Interview 34 (Big Pharma)):

- *Lack of speciality and formation of closed policy networks*

  Even as recently as about 10 years ago, Korea had no experience with institutions for fostering new drug R&D, including regulation and approval; the government essentially imitated the US FDA when establishing the relevant laws and rules. However, the administrative process by the civil service has been implemented with no experience or understanding of the global pharmaceutical industry, through armchair arguments.[120]

  Policy makers have suffered from a lack of knowledge of the industry and technology, and therefore they relied on professors. Thus, professors have become the most influential community in the design and operation of the relevant S&T policies and NRDPs. As most professors were involved in upstream research, the support of scientific research was their main interest, putting aside the potentiality of industrial development.

- *The combined effect of the incentive structure and the closed policy network*

  Professors are in a kind of king's position in Korea. They are best at doing scientific research rather than practical drug R&D, and their interest is generally directed at receiving more R&D funds and publishing papers. Few of them consider their opportunity to contribute to the industrial sector, and only a small number of experienced professors have any knowhow about the interrelationship between academia and industry. In this country, although the relationship is not actively hostile, it is like oil and water: Professors and industry have not interlinked well.

[120] A similar comment was made by Dr Chang-ho, Ahn, the CEO of Rexahn Pharmaceuticals in the US: 'Civil service in Korea lacks expertise. In the US, many civil servants work in the same field for a long time, 10 to 20 years. By contrast, in Korea, many policies are practically designed by 5th-grade junior officials (the position between 1st and 9th grade) who just graduated university' (3/5/2013, Korea Economic Daily).

> Under this culture, policy makers, who are informed by the academic community, easily come to conclude that if they supported biotechnology-based upstream research, new drugs would be automatically developed.

The stem cell research scandal on Dr Hwang's research team in 2006 can be seen as a negative result of the closed policy network between policy makers and a small number of professors under short-term, performance-based evaluation pressure.[121] Similar comments were made by the CEO of a DBF, Proteogen, who returned to the country in 1974, drawn by the government policy to attract overseas Korean scientists (Interview 20 (DBF)).

> What has long been misunderstood in Korea is the belief in the direct commercialisation of the scientific work published in *Nature* or *Science*. These magazines are for acquiring legitimacy of new knowledge, not technology. That is to say, a knowledge validation process is needed to further develop technology from knowledge. However, until recently, researchers and professors doing genetic engineering have misunderstood/misled that laboratory-based experimental performance can be easily scaled up and commercialised. Moreover, governmental R&D support to universities has been mainly produced and evaluated in publications. In this atmosphere, academics have tended to have an exaggerated belief that their research results would soon be on the market. This led to more R&D support.

These remarks reveal that the underlying mechanism behind these problems is the deteriorated and inefficient NRDP resource allocation process, created by an implicit relationship between policy makers and a small number of professionals in the S&T area. Related to this, the CEO of a DBF pointed out that the dominance of professors in the selection mechanism has been a main reason for the fragmented allocation of national funds by NRDPs to universities (mainly for publications) and GRIs with no practical experience in new-drug development (Interview 33 (DBF)).[122]

In the national promotion of biotechnology, academics and many DBFs seldom needed to acquire R&D funds and projects from the pharmaceutical industry since funding

[121] Based on the critics of a professor in Aju University, of the close relationship between star scientists and policy maker, blog post (http://bric.postech.ac.kr).
[122] He appraised that the direction of overall S&T policy of biotechnology and NRDPs toward strengthening upstream research was the right decision.

through NRDPs met minimal funding requirements for operating their research (Interview 38 (Big Pharma)).

Summarising remarks

The closed policy network between civil service and professors has continued to act as the dominant decision-making group in directing S&T policy and selecting NRDPs. As seen above, this institutional structure stemmed from the previous imitation period for effective resource allocation, and still underlies the recent innovation-oriented S&T policy and NRDPs (Park et al. 2005, Jung 2007). Consequently, biotechnology-oriented upstream research led by public actors (i.e., universities and GRIs) and DBFs has been the main beneficiary of the NRDP selection environment. Combined with the PBS incentive system, this has led to a high concentration of upstream and public biotechnology research in NRDPs, resulting in the relative segregation of technologically conventional synthetic-drug-based and downstream development oriented pharmaceutical firms from the rapidly increasing biotechnology-related NRDPs.[123]

5.4 Ministerial Role of Supporting New-drug R&D

This section addresses the macro-level administration pattern of NRDPs by three leading ministries in supporting new-drug R&D and its industrialisation: MOST, MOHW and MOTIE. It describes a number of underlying institutional problems in the three ministries that prevent the efficient implementation of S&T policies, such as compartmentalisation of R&D support.

This section first discusses the macro-level administrative pattern surrounding R&D support, including ministerial leadership in S&T policies and the governance structure of GRIs (Sub-section 5.4.1). The substantial role of each ministry is then explained (Sub-sections 5.4.2, 5.4.3 and 5.4.4, respectively). Lastly, the ministerial policies for drug R&D support are summarised (Sub-section 5.4.5).

5.4.1 Governmental structure of drug R&D support

The first round of NRDPs for drug R&D were mostly carried out by MOST and MOHW (Table 4.6 and Figure 5.3). At that time, the division of supplying NRDPs between the two ministries had operated relatively well because of the relative simplicity of R&D activities in the beginning stages of new-drug R&D, and thus the relatively low demand

[123] A summary of comments on the selection problems of NRDPs is given in Appendix 6.

for NRDPs by industry.[124] Interestingly, the ministries launching drug R&D programmes had begun to diversify in the 2000s, with a rapid increase in the total amount of R&D funding that each ministry could disburse (Figure 5.3). In particular, MOST, MOHW and MOTIE became the leading ministries for biotechnology and drug R&D support among 10 relevant ministries.

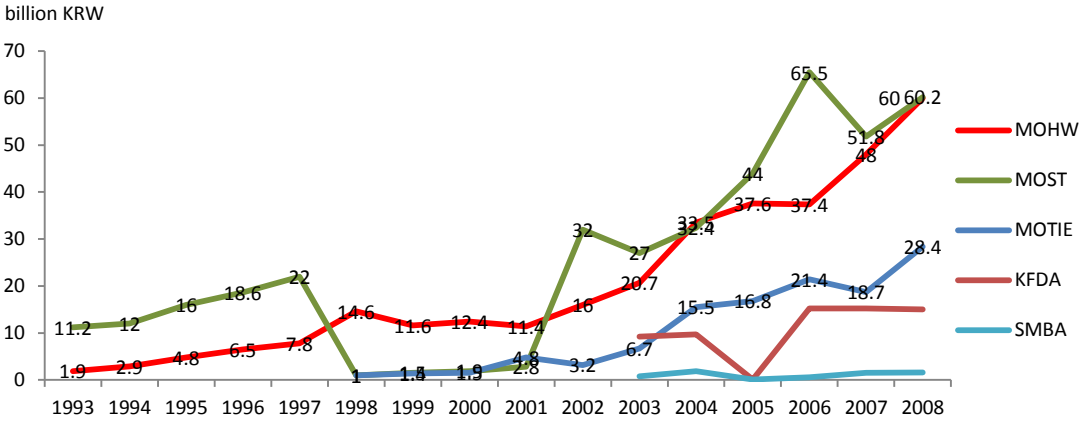

Figure 5.3: Amount of drug R&D funding support by ministry

Source: Data from KHIDI Survey reports (2005, 2008, 2009)

The other administrative change has to do with the establishment of the research council system. In 1998 under the national effort for the transition, the governance structure of GRIs was reformed to a research council system; this came alongside a change in the incentive structure to the PBS. The research council system was introduced to broaden administrative autonomy and reorient the mission (Yim and Kim 2005). However, the research councils have no authority in the compilation of budgets or in personnel management. Thus, GRIs have to deal with a dual administration structure with an on-going lack of independence and autonomy (Figure 5.4). This structure also shows the priority of the umbrella organisations in allocating NRDPs such as GRIs (Kim 2000).

The following sub-sections address the pattern of policy implementation by the three leading ministries in supporting new-drug R&D: MOST, MOHW and MOTIE.

[124] Specifically, the domestic firms accumulated the basic experience in upstream research through participating NRDPs established by MOST (e.g., HAN Project and Special R&D programme). At the same time, the pharmaceutical firms' drug R&D directly benefited from NRDPs both for process innovation (i.e., localising process technologies) and product innovation (e.g., developing IMDs or NCEs) by the Health Technology Programme launched by MOHW (Interviews 45, 47, 48 and 52 (K-Pharma)).

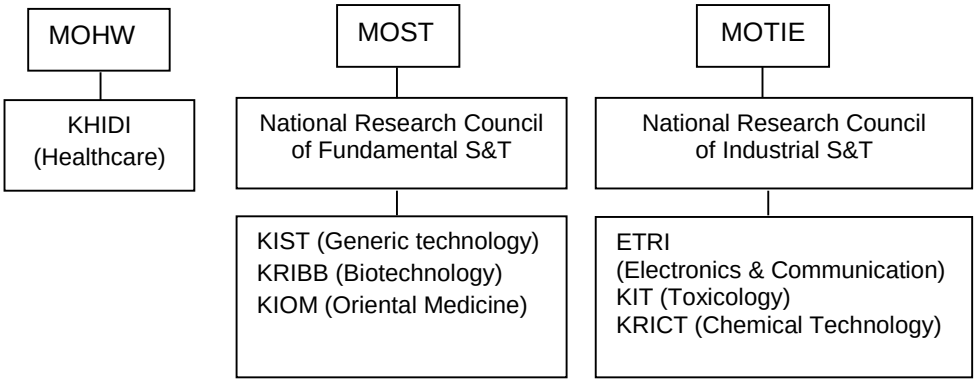

Figure 5.4: Governance structure of GRIs surrounding new-drug R&D

Source: Modification from STEPI Report (2008)

5.4.2 Ministry of Science and Technology (MOST)

1) Supply pattern of NRDPs: Prioritisation of public research actors

MOST has acted as the main supplier of NRDPs since the early stage of drug R&D; 61% of total drug R&D funding by the government to GRIs (and 49% of funding to universities) was disbursed by MOST in 2004.[125] The GRIs directly administered by MOST and a few privileged universities have been prioritised in receiving NRDPs.

For example, all eight Frontier Programmes, the largest NRDPs related to biotechnology and drug R&D, have been allocated to the two umbrella GRIs, KRIBB and KIST, and two universities (Table 5.4).[126] Each programme operates a number of projects. KRIBB took charge of three Frontier Programmes, and the other two were led by KIST.

Overall, the priority of GRIs in NRDPs has been maintained; there has also been an increasing proportion of universities in the last two decades. On the one hand, this pattern of R&D support is justifiable in that the main goal of the ministry is to strengthen upstream research capability; hence, it is perhaps inevitable that public research organisations will dominate. On the other, the high proportion of NRDPs that go to a relatively small number of public institutes and universities implies the relative exclusion of other public research and industrial actors.

[125] They provided 308 projects under 31 NRDPs for drug R&D in 2008 and many programmes involved are mission-oriented led by GRIs (e.g., Frontier Programmes and Biotechnology R&D Group for biologics and organs).
[126] KRIBB: Korea Research Institute of Bioscience and Biotechnology (since 1990), KIST: Korea Institute of Science and Technology (since 1966). Frontier Programme: the NRDP invest about US$10 million every year for each programme for 10 years. Another one has been led by the Korea Research Institute of Chemical Technology (KRICT) under MOTIE.

Table 5.4: Frontier R&D programmes for biotechnology

Programme	Programme leader	Period
Intelligent Microsystems	KIST	1999~2010
Functional Analysis of Human Genomics	KRIBB	1999~2010
Plant Diversity Research	KRIBB	2000~2010
Crop Functional Genomics	Seoul National University	2001~2011
Biological Modulators Research	KRICT (Chemical technology)	2001~2011
Stem Cell Research	Yonsei University Medical Centre	2002~2012
Microbial Genomics and Applications	KRIBB	2002~2012
Functional Proteomics	KIST	2002~2012
Brain Research	Seoul National University	2003~2013

Source: Website of each R&D programme

2) Problems: Limited role of private innovation actors in NRDPs

The role of private innovation actors has been limited by this administration pattern. In 2010, only 14% of NRDPs for biotechnology and drug R&D were led by a firm as the programme/project leader (NSTC 2010). Private firms, DBFs and pharmaceutical firms have mainly participated in the NRDPs as contractors of individual projects under GRIs or universities, which, in many cases, serve as programme leaders (see Table 5.5). This public actor orientation of NRDPs has, to a large extent, limited the active participation of industrial actors in the NRDPs and impeded commercially viable innovation (the PBS incentive structure and professor-based selection environment have also contributed to this problem).

For the DBFs, as the main recipients and often the final (sub)contractors of the NRDPs, the operational pattern of NRDPs led by MOST has considerably disrupted their R&D activities. They have participated in NRDPs with the aim of complementing deficient internal R&D funds. However, their original R&D activities are often delayed or disrupted by the public actor-centred evaluation system of the NRDP, which privileges publications.

More specifically, the beneficiary DBFs are forced to produce their R&D products through publications (Interviews 5, 8, 12, 17, 20 and 36 (DBF)). DBFs interviewed point out that the publication-oriented selection and evaluation criteria do not reflect the characteristics of business-oriented scientific research. However, national R&D funds are relatively abundant, while investment from the pharmaceutical industry is fairly poor. Given this

situation, as many DBFs have still been struggling to survive, they have been eager to take part in NRDPs.

Table 5.5: Projects in the biotechnology-related Frontier Programme broken down by programme/project leader

Programme (Programme leader)	Universities	GRIs	Industry
Microbial genomics and applications (KRIBB)	40 projects as the project leader (in total 151 participating projects)	25 (96)	DBFs - 4 K-Pharma -1 *Chaebol* - 3 (56)
Functional proteomics (KIST)	75 (75)	20 (20)	DBFs - 7 (36)
Functional analysis of human genome (KRIBB)	65 (95)	28 (28)	DBFs - 4 K-Pharma -2 *Chaebol*- 2 (15)
Plant diversity research (KRIBB)	91 (165)	37 (58)	DBFs - 14 K-Pharma - 2 *Chaebol*- 4 (118)
Stem cell research (Seoul National University)	131 (169)	5 (13)	DBFs - 9 K-Pharma - 3 (50)
Total number of projects	402 (655)	115 (215)	DBFs - 38 K-Pharma -8 *Chaebol*- 11 (265)
The proportion of main projects	61.3%	53.5%	21.5%

Source: Data from programme websites and White Papers of the Frontier Programme 2010 and 2012

This has resulted in the DBFs relying excessively on the NRDPs rather than seeking to supply innovation sources (e.g., promising drug candidates) to the pharmaceutical industry (Interview 38 (Big Pharma)). This was despite recognising the negative effect of public actor-centred, single-mode evaluation (i.e., the focus on publications) on their main R&D targets. As a result, while the upstream research performance in NRDPs has seemingly been strong, the programmes have undermined private actors' identity as industrial developers (Interview 20 (DBF)).

For pharmaceutical firms, as noted, there is an increasing need for external innovation sources from public upstream research due to weak internal research capability. However, even if they feel the project is attractive, they are concerned about becoming a sitting target when they join a NRDP because they are required to paying matching funds (50%) for project expenditures (Yakup Newspaper, 16/7/2007). Most participants

in NRDPs are GRIs and universities with different incentive bases, and the firms fear that they might be used only as financial sources for public sector upstream research rather than acquiring industrially useful research outcomes and complementing drug R&D costs. Firms could also be hesitant to join a NRDP due to the potential for conflict with GRIs over the ownership of patents (*ibid.*).

In addition, in terms of the industrial potential of public actor-led drug R&D projects, a CTO in a leading pharmaceutical company criticised the amateurism of GRIs, which often try to develop new drugs on their own (Interview 51 (K-Pharma)).[127] He pointed out the complexity of commercially viable new-drug R&D compared to upstream research, and said that GRIs often fail to consider business dynamics because they are overconfident about the potential of academically trendy research topics.[128]

Overall, the dominance of public actors in both designing and conducting NRDPs has discouraged the active participation of pharmaceutical firms.

3) Summarising remarks

On the whole, the NRDPs administered by MOST have focused on biotechnology-based upstream research such as understanding biochemical mechanisms and discovering new bio-materials. Public innovation actors such as GRIs, universities and DBFs have been the main recipients of the various NRDPs administered by MOST. These NRDPs have been implemented in line with MOST's ultimate policy goal of strengthening scientific research capability, and thereby contribution to innovation under the Biotechnology Promotion Act. However, in spite of the acknowledgement of the necessary role of pharmaceutical firms in national drug R&D projects (MOST 2006), the dominance of public actors in the operational mechanisms of NRDPs has disrupted effective relationships with pharmaceutical firms through NRDPs.

[127] For example, a recent NRDP, namely the derivation of disease-based drug candidates, with the aim of technology transfer of drug candidates to private firms, selected three GRIs (KIST, KRIBB, and KRICT) in 2007. Although the inter-GRI project leader was scouted from a private firm, LG Life Science, no pharmaceutical firm was put in this project as a main subject.

[128] Similarly, the CEO of Crystal Genomics developing NCEs criticised the attempt to directly lead new-drug development by GRIs, which have no experience or knowhow of the drug business.

5.4.3 Ministry of Health and Welfare (MOHW)

1) Supply pattern of NRDPs: Supporting firms' survival and the production of generic drugs

Since the middle of the 1990s, MOHW has increasingly played a role as another main supplier of NRDPs; this has led to the diversification of drug R&D support across ministries (Figure 5.3).[129]

Unlike MOST, MOHW has had a tendency to support industrial-side R&D as well as public sector research. The Health Technology Programme launched by MOHW is administered by a single umbrella organisation, the Korea Health Industry Development Institute (KHIDI), which was established in 1999 to nurture the health industry. In 2004, about 70% of the total drug R&D funding to pharmaceutical firms was disbursed by MOHW (Trend of Healthcare Technology, 2006). In terms of performance, 83% of new drugs developed by domestic firms were partially supported by the NRDPs of MOHW (Yeo 2011).

This Health Technology Programme for drug R&D administered by KHIDI has operated in a small-scale manner (i.e., as seed money in widely-fragmented small projects). For example, 174 projects in all were selected in 2006 under the Health Technology Programme. However, each project was only granted around US$10,000, although two clinical trials were granted about US$1 million.[130]

In the first round of innovative R&D in the 1990s, this type of operating pattern contributed to broad feeding of domestic firms with minimum R&D funding (Interview 35 (DBF)). This is due to the greater responsiveness of the Health Technology Programme to demand from the industry, as opposed to the mission-oriented, large-scale and public-actor-supportive NRDPs of MOST. Pharmaceutical firms could submit their own proposals to participate in an NRDP, utilising the funding as seed money for a R&D project. This was one of the main reasons for the relative balance between supply and demand patterns of NRDPs for drug R&D in 1990s.

Overall, a small-scale but widely distributed Health Technology Programme was implemented to support the survival of the domestic pharmaceutical industry as a

[129] The diversification of administrative leadership was not a special case for drug R&D, but a general institutional change in the country, as we can see from the case of the leadership of the Ministry of Information and Communication (MOIC) for ICT-related NRDPs at that time.

[130] Although, in the changing S&T policy for drug R&D, the size of funding started to increase in the late 2000s, it is a very recent phenomenon.

production base for cheap and high-quality generic drugs, leading to cost savings for the NHI (Interviews 14 (*Chaebol*), 9 and 20 (DBF) and 34 (Big Pharma)).[131]

2) Problems: The lack of innovation context in the support to firms' survival

While MOHW's pattern of R&D support was appreciated by the industry, pharmaceutical companies have increasingly demanded more active R&D support for new-drug R&D in the 2000s. Their needs have become more sophisticated and diversified across the various R&D steps, from drug identification to clinical trials, depending on each firm's R&D level (Interview 42 (K-Pharma)). As MOHW has acted as the leading ministry providing direct support to pharmaceutical R&D, new demands have been directed to MOHW.

However, MOHW has also failed to meet recent industrial needs. The MOHW's lack of consideration of industrial competitiveness is the main reason for its passive response to changing demand patterns of NRDPs. That is, the policy consideration of industrial upgrading and innovativeness has been subjugated to the support of the industry within the NHI frame. This has been pointed out by both pharmaceutical firms and emerging DBFs.

> Although MOHW has recently launched a division for fostering the healthcare industry, they have treated the pharmaceutical industry as a simple production sector for supplying cheap drugs (for the stable management of the NHI). The healthcare sector is a very extensive sector including pharmaceuticals, public health service, and so on. They didn't count the pharmaceutical sector as a significant industry ... With a lack of industrial mind-set, their R&D support has been implemented in dispersed fashion, mainly in line with the efficient production of generic drugs. The pricing policy, which is excessively favourable to generic drugs, guaranteeing about 80% of the original drugs' prices, has come to be a signal for the domestic firms to discourage new-drug R&D (Interview 34 (Big Pharma)).

In other words, instead of innovation facilitating policy for industrial upgrade, generic-drugs-supportive policy under the NHI has acted as the only pulling factor from the market. In recalling the overall commercial failure of the domestically developed NCEs, one interviewee said

[131] According to von Tunzelmman's (2010) term.

> The government introduced the product patent system very early, and thus several domestic companies have developed new drugs. However, the outcome of the R&D was not protected in the domestic market due to the generic-drug-supportive pricing policy and … the KoPI became a crippled industry (Interview 38 (Big Pharma)).

Increasing complaints about the absence of industrial policy by the ministry were expressed by industrial actors, which sought to transfer the jurisdiction of the Korea Pharmaceutical Manufacturers Association (KPMA) from MOHW to MOTIE in the expectation of more active industrial support by MOTIE (Daily Pharm, 11/5/2011).

Similar criticisms were identified by the biotechnology sector. The CEO of the first DBF in Korea, Bioneer, pointed out the lack of industrial mind-set in MOHW (Interview 9 (DBF)):

> The administrative leadership of biotechnology in Korea has belonged to MOHW because of the juridical right of regulation and approval. MOHW's problem is that it has no experience in fostering an industrial sector, and thus its mind-set is different from that of MOTIE, which has spearheaded the government-led industrialisation of Korea. Regulation and approval systems have been formed with little consideration of the industrial level and competitiveness.

Although his remarks can be regarded simply as a kind of complaint about the biotechnology business in Korea, there is a notable absence of consideration of industrial innovation in the ministry that has also been widely criticised by the pharmaceutical industry. However, at the same time, it should be noted that the main policy goal of MOHW is the stable management of the public health service.

3) Summarising remarks

Overall, the R&D funds from MOHW have been used largely as seed money, not for industrial innovation, but to support the producers of generic drugs for the efficient management of the NHI. As a positive outcome, the KoPI's chemistry-based synthetic drug R&D was able to get the support to upgrade production capability. However, with the lack of industrial policies, R&D support from MOHW has not met the industry's evolving demand for NRDPs, such as more large-scale and market-reflective R&D support for the development of innovative drugs.[132]

[132] The author does not disagree with the fundamental role of MOHW as the regulator of the public health sector. However, on the other hand, in terms of the sustainability of the semi-public industry, there must be

5.4.4 Ministry of Trade, Industry, and Energy (MOTIE)

1) Supply pattern: Emerging biotechnology-oriented industrial support

MOTIE began to support the country's fledgling biotechnology industry on the basis of the Plan for Fostering Biotechnology Industry in 1994. In 2001, just after the recovery from the Asian financial crisis, the government chose the biotechnology industry (referred to as 'BT') to be one of six next-generation growth engines (HeraldBiz, 17/1/2013). Since then, MOTIE has expanded its administrative scope.

In line with this, MOTIE's policy focus has been mainly to bring up DBFs. It started a certification system for so-called 'bio venture' companies, and the certified venture firms have benefited from both participation in NRDPs and tax breaks (Table 5.6).[133] It also supported the construction of regional biotechnology clusters, although the policy has caused duplication of R&D investment (e.g., techno-parks and technopolises).[134] That is, MOTIE is fostering biotechnology start-ups to further its ultimate policy goal, the industrialisation of biotechnology.

Table 5.6: Number of new DBFs by year

Year	1995	1996	1997	1998	1999	2000	2001
Number of new DBFs	19	14	27	36	71	233	200

Source: DBFs Survey by the Ministry of Commerce, Industry and Energy in 2001

MOTIE is now broadening its supportive scope, mainly focusing on commercial development. Several large-scale NRDPs have been launched, such as the Bio-Star Project in 2005 and the New Growth Engine Projects in 2009 (Table 5.7). The Bio-Star Project was established to develop biotechnology-based commercial drugs (i.e., innovative biologics, biosimilars, stem cell therapy and converging technologies between biotechnology and ICTs).[135]

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a certain role as an institutional promoter of developing new drugs by local companies for a cheaper and effective new drug supply for the people. Without the existence of local new drugs, the market dominance by a small number of Big Pharma firms would continue. Many developing countries are already facing many negative effects of this dominance, such as import cost, lack of appropriate drugs for locally common diseases, and further deficit of the national health system.

[133] Many leading DBFs were established in the period, such as Viromed (1996, drug R&D), Macrogen (1997, genomic R&D), and Crystal Genomics (2000, drug R&D). Bioneer, Viromed and Crystal Genomics have been published by the preferential system of a company having core technologies without proving the record of market performance by first registering in the Korea Securities Dealers Automated Quotations (KOSDAQ) in 2005, while Macrogen was the first IPO company as DBF in 2000.

[134] It is now estimated that a total of 34 bio-clusters are now being operated, mostly by regional governments, and the duplication of investment has been criticised (Kim, 2011).

[135] It, on average, supports about US$1 million annually for five years based on the annual evaluation system and matching fund style.

In terms of the authority in charge of drug R&D, a division administrating the biotechnology industry was first articulated in 1998 as a division of the chemical and biological industry under the life industry. In 2011, MOTIE established a new division of bio-health that was responsible for strengthening the promotion of biotechnology industrialisation and medical service-related industries in earnest.[136] This indicates an expansion of the ministry's administrative scope in the industrialisation of biotechnology beyond the chemical industry, with increasing R&D investment.

Table 5.7: Main fields of the major R&D programmes by MOTIE

Name of NRDP	Main technological fields supported
Bio-Star	· Innovative biologics – Antibody, stem cell and gene therapy · Partly NCEs and phytomedicines (since 2008)
New Growth Engine	· Antibody drugs, stem cell therapy, gene therapy drugs (Core-tech)
	· Commercialisation of biosimilars and their export (Infrastructure) · Biotechnology based contract research organisation (CRO) and contract manufacturing organisation (CMO), production base of bio-drugs · Support for the clinical trial base for bio-drugs

Source: Various data sources

2) Problems: Capability in implementing industrial policy in the science-based industries

However, while MOTIE has focused on the industrialisation of emerging biotechnology in the past decade, the established, chemical-synthesis-based pharmaceutical industry has been barely comprehended by the ministry's promotion of biotechnology-oriented commercialisation support. That is, the overall policy pattern of MOTIE toward emerging biotechnology in practice hardly considers the role of the established pharmaceutical industry for biotechnology industrialisation.

> MOTIE has been drawn to support emerging biotechnology and its industrialisation. Their focus on commercialisation was a step in the right direction, given the upstream research-oriented support by MOST. However, MOTIE has hardly recognised the importance of the pharmaceutical industry as the final gate for biotechnology industrialisation... (Interview 34 (Big Pharma)).

[136] In this line, MOTIE started to gradually comprehend the development of the phytomedicines and NCEs, in keeping with the new biotechnology-oriented industrial policy.

This poses another risk that national resources will be overly concentrated on the emerging new technologies that have a high degree of uncertainty in terms of both technology and market.

> Although in the long-term view, biological drugs will definitely supplant the present chemistry-based drugs, the latter type of drugs are still far more dominant in the pharmaceutical market, and this trend will continue for a long time. However, in spite of that technological stability and the regulatory environment of biological drugs, even biosimilars, is still estimated to be opaque, the government seems to deliver their institutional efforts only to biotechnology (Interview 42 (K-Pharma)).

In reality, since 2010, biosimilars (and the stem-cell business) have (re)gained governmental attention as the most promising biotechnology businesses. Samsung Biologics was selected as the main player for developing biosimilars under the New Economic Growth Smart Project in 2009, despite the absence of any previous industrial experience in the area. In 2011, the country approved a novel stem cell therapy, followed by two more stem cell therapies in 2012, although concerns about their safety have been constant. Celltrion has been the largest company listed on the Korea Securities Dealers Automated Quotations (KOSDAQ) since 2009, even though it has not shown clear profit realisation of its business model in biosimilars. The company acquired the world's first approval of its monoclonal antibody biosimilar in Korea in 2012.

Related to this, interviewees who conduct chemical drug R&D were sceptical of the commercial possibility of stem cell-based therapy in the short- and medium-term.[137] In addition, they regard the industrial support of biosimilars with the aim of taking global market leadership through mass production as a 'policy bet' due to technological instability, an immature market (only a few biosimilars had launched as of 2012) and regulatory uncertainty.

3) Summarising remarks

On the whole, MOTIE has actively driven the industrialisation of emerging biotechnology by launching development-oriented NRDPs, fostering DBFs and attracting *Chaebol* to the new industrial area. However, in spite of these active efforts in biotechnology, the incumbent pharmaceutical industry was hardly included in MOTIE's policy implementation. The reason lies in MOTIE's misunderstanding of the role of the established pharmaceutical industry as the commercial channel when they fostered the

[137] Among them, one of most pessimistic views was the impossibility of the 'real' commercialisation of stem cell therapy within 10 years.

upstream research-based biotechnology business. At the same time, the established pharmaceutical industry has been regarded as the juridical right of MOHW.

Table 5.8: Inter-ministerial comparison of institutional momentum

	MOST	MOHW	MOTIE
Policy goal	Scientific capability as innovation source	Sustaining stable NHI for public health	Biotechnology as next economic growth engine
Fundamental law	Biotechnology Promotion Act (1983)	Health Technology Promotion Act (1995)	Biotechnology Promotion Act (1994)
Technological focus	· Upstream research	· Efficient production · Pre/ clinical trial	· Clinical development
Main recipients	· GRIs and universities · DBFs	· Universities, GRIs · Pharmaceutical firms	· GRIs · *Chaebol* and DBFs
Role practiced	Biotechnology-oriented public research support	Focus on survival support of generic drug producers	Biotechnology-oriented development support

Source: Author's elaboration based on various data sources

5.4.5 Summary of the ministerial role

The three leading ministries involved in drug R&D have reinforced their administrative leadership to further each ministry's own goal (Table 5.8): for MOHW, developing high quality generic drugs to ensure the stable management of NHI; for MOST, bolstering the scientific research capability of public primary actors in biotechnology; and for MOTIE, supporting the industrialisation of biotechnology.

On the one hand, the inter-ministerial diversification of R&D programmes and the ministries' different policies make sense, given their different goals. However, in the view of the KoPI, no ministry has directly met the changing demand patterns of NRDPs, even though the three ministries have strengthened national resource input to drug R&D and its industrialisation in the category of biotechnology.

5.5 Effect of Policy Dynamics on Drug R&D Practices

The start of this section traces the outcomes of the problematic operational mechanism of NRDPs surrounding new-drug R&D (Sub-section 5.5.1). It then briefly reinterprets the operational mechanisms of NRDPs in view of exploratory learning (Sub-section 5.5.2). It implies a mismatch between the institutional revisions and the nature of exploratory learning.

5.5.1 Expressed outcomes of the policy dynamics

1) *Overlapping R&D investment and high success rates of research projects*

Two related phenomena caused by the operational mechanism of NRDPs are over-competition to acquire more support among public innovation actors and overlapping NRDP investment.

As seen, the PBS-based incentive structure has led public actors to acquire more projects in a risk-averse fashion. It has forced public actors to propose many similar research projects within a few popular research areas. Under the prioritisation of umbrella research organisations by the ministries, these projects were launched without a thorough investigation of dual R&D investment. An officer of the Ministry of Strategy and Finance (MOSF) expressed the difficulty of the budgeting involved in biotechnology and new-drug R&D:

> Each ministry [MOHW, MOST and MOTIE] asks for a budget allocation for own biotechnology investment every year… Although we recognise it is overlapping investment, we inevitably accept their requests to a certain extent because of the sectoral speciality (Yakup Newspaper, 23/10/2001).

In 2004, the government tried to clarify the division of R&D support between ministries; for example, MOHW dealt with clinical trials and MOST dealt with upstream research. However, soon after the inter-ministerial coordination agreement, each ministry again began to compete in launching drug R&D projects (Interviews 2 (university) and 20 (DBF)]. Ministries have continued to expand their administrative power in the enlarging biotechnology and new-drug R&D sectors.

NSTC has acknowledged the overlapping investment of national R&D funds in drug R&D; at one point, 21 public institutes (mostly GRIs and universities) were found to be conducting similar drug R&D projects (Yonhap News, 1/8/2011).[138] At the same time, it should be noted that most NRDPs, designed to promote innovative research, were counted as successful projects. As noted, in 2010 about 95% of all NRDPs were reported to have resulted in the successful completion of their projects. This indicates a high level of risk aversion in conducting research projects or choosing research projects in the first place (See Sub-section 5.3.1.2).

[138] The National Assembly Budget Office pointed out the seriousness of an overlap in NRDPs of biotechnology-based drug R&D between ministries as one of the representative cases of dual investment (NABO 2009).

2) *Tension between industrial communities surrounding R&D support*

The operation pattern of NRDPs also triggered competition between DBFs and pharmaceutical firms in acquiring more national R&D support. DBFs have, to a large extent, relied on governmental support for their survival rather than utilising pharmaceutical companies. Meanwhile, the demand for R&D support from pharmaceutical firms has also rapidly increased due to their weak financial base.

While the tension between the two industrial communities had long been latent under the rapid increase in national R&D investment in biotechnology, with its some benefits for pharmaceutical firms, it eventually came to a head in 2011 with the re-emergence of the industrial policy for promoting the pharmaceutical firms' new-drug R&D, the Pharmaceutical Promotion Act. The conflict was exposed through the controversy between relevant industrial communities.

While the promotion act had been one of the main institutional demands by the pharmaceutical industry since the 1990s (Interview 42 (K-Pharma)), for the biotechnology communities that concentrate on upstream research, the policy was regarded as a potential threat that could undermine national support for biotechnology R&D due to the limited national R&D funds. In line with this, the Biotechnology Association of Korea, the largest industrial association of DBFs (under MOTIE), came out against the act (Health Korea News, 11/3/2009). The Biotechnology Association argued that the Biotechnology Promotion Act had already been in place for the last decade as the comprehensive supportive policy for the industry, and that the new Pharmaceutical Promotion Act would overlap with the Biotechnology Promotion Act (*ibid.*). Moreover, it claimed that the Pharmaceutical Promotion Act should be coordinated by other concerned ministries, not only led by MOHW (*ibid.*).

The Korea Drug Research Association (KDRA) refuted this, arguing that the Biotechnology Promotion Act was meant to facilitate R&D activities while the new act aimed to strengthen comprehensive industrial competitiveness, such as by giving preferential treatment in NHI drug pricing to firms with high R&D intensity. The KDRA further demanded more transparency in the performance relationship between R&D funding support and industrial outcomes under the Biotechnology Promotion Act (Pharm 21, 11/3/2009). In particular, the KDRA pointed out that, in fact, national R&D funds had been limitedly flowing into the pharmaceutical industry under the Biotechnology Promotion Act (Interview 42 (K-Pharma)).

Underlying the tension seems to be a longstanding distrust between pharmaceutical firms and DBFs that disrupts active R&D collaboration. The pharmaceutical firms have tended to depreciate the value of research outcomes of DBFs and public actors due to the need for further development with large-scale investment, while the DBFs and public actors have tended to exaggerate the commercial potentiality of the research outcomes.

Moreover, in the absence of a real industrial policy on the part of MOHW, there have been increasing complaints by the industry that the jurisdiction of the Korea Pharmaceutical Manufacturers Association (KPMA) should be transferred from MOHW to MOTIE, since MOTIE prioritises industrial support. By doing so, once KPMA becomes an umbrella industrial association of MOTIE, the industry can expect more industrial support (Daily Pharm, 11/5/2011). At present, it seems to compete for institutional leadership to influence the direction of biotechnology and new-drug R&D support under the different jurisdictions of each ministry (MOHW – KPMA and MOTIE – Biotechnology Association of Korea).[139]

On the whole, these cases show that the problematic allocation and management of NRDPs has caused intensified competition among industrial actors that in theory should have been collaborating on successful drug discovery and its commercialisation.

5.5.2 The policy dynamics in view of exploratory learning

As a result, effective exploratory learning seems to have been difficult under the operational mechanisms of NRDPs. A publication-oriented and risk-averse tendency among public innovation actors and DBFs has become common in conducting NRDPs under the PBS. The professor-led selection environment has tended to prioritise their research interests in upstream biotechnology research, which might be better suited to academic publication than innovation viability. Moving forward, the fragmentation and competition of administrative leadership in new-drug R&D and biotechnology across the three leading ministries has also failed to link upstream, biotechnology-centred R&D support to pharmaceutical firms' industrial R&D. In other words, exploratory learning among public innovation actors and inter-organisational exploratory learning have been disturbed under the current policy dynamics. The effect of these policy dynamics on innovation actors' exploratory learning will be discussed in depth in Chapter 8.

[139] Korea Biomedicine Industry Association: a new industrial society approved by KFDA. It consists of several *Chaebol* affiliates and operates a biotechnology based drug business (e.g., CJ, Samsung Electronics, SK Chemical), several leading DBFs (e.g., Celltrion and Viromed), and a few multinational companies (e.g., GSK and Sanofi Pasteur).

5.6 Summary

This chapter has examined the effect of S&T policies on innovation actors' new-drug R&D by analysing the operational mechanisms of NRDPs in view of exploratory learning, which was conceptualised as the key mode of technological learning for new-drug R&D.

First, the analysis found that the PBS, as the main incentive system of NRDPs, has caused grave side effects on R&D practices, such as an overemphasis on short-term and quantitative research performance (e.g., the number of publications). While the macro-level landscape of national S&T policies is oriented to innovation generation, the micro-level evaluation system has driven institutional contradictions in promoting research for innovation generation among public organisations.

Second, the selection environment of NRDPs, which is dominated by academics and civil servants, a closed policy network, has created a reinforcing mechanism for the publication-oriented incentive pattern in upstream biotechnology research, with little consideration for industrial potential.

Third, the administrative pattern of NRDPs showed that the three leading ministries (MOST, MOHW and MOTIE) have rapidly increased support to the biotechnology industry, including new-drug R&D. However, the ministries are uncoordinated and have limited administrative ability to interlink their various NRDPs under their different policy goals.

On the whole, this chapter showed that the revised S&T policies aimed at innovation generation are defective in promoting innovative R&D. In view of exploratory learning, these policies can be seen as inhibiting risk-taking and collaborative R&D for industrially meaningful new-drug development. That is, the operational mechanisms of NRDPs seem to convert ample resource investment and learning effort into vague industrial performance.

Chapter 6: Firms' Exploratory Learning in New-drug R&D

> New drug development itself, in retrospective view, became the ultimate goal of the new drug R&D by the domestic firms. Their first new drugs can be regarded as the preparation process for the real new drug R&D which just started nowadays, not as a sincere new drug R&D with thorough development strategy (Dr Ku-chan Kim, the science ambassador of MSD).

6.1 Introduction

This chapter investigates Korean pharmaceutical firms' new-drug R&D activities over the past 25 years, with the goal of understanding the exploratory mode of technological learning that is performed by latecomer firms. The investigation is based on the conceptual framework of a firm-level learning pattern transformation that allows a company to develop more innovative drugs beyond imitative generics. Ultimately, this chapter argues that new-drug R&D itself does not guarantee successful catch-up if a firm's intensive learning does not reflect the key characteristics of the exploratory mode of technological learning and changed competition environment in the transitional phase.

As noted in the methodological chapter (Chapter 3, Sub-sections 3.5.1.2 and 3.4.2), the empirical analysis has drawn on new-drug R&D projects of nine Korean firms. The new-drug R&D projects were analysed across two transitional rounds. The first round of new-drug R&D, which spans a period from the late 1980s to the early 2000s, consists of a series of early projects that failed to commercialise, and some later successful projects that created the case firms' first NCEs. The second round of new-drug R&D projects includes recent projects that started from the middle 2000s in an effort to reconfigure the previous new-drug R&D pattern.

For both rounds of new-drug R&D, the empirical analysis is reported in two stages: a description of a specific firm or project case, and then an overall presentation of other aggregated cases to support the representative case. This approach is used to avoid the risk of over-complex description. Moreover, data on new-drug pipelines in about 30 pharmaceutical firms are partly drawn upon to confirm the drug-R&D pattern in the KoPI.

Prior to the main analysis, the present technological level and market position of the case firms are presented (Section 6.2). Section 6.3 identifies the R&D process, strategy and marketing pattern in the first-round new-drug R&D. The subsequent section (6.4) investigates the case firms' recent reconfiguration of new-drug R&D that was triggered

by previous commercial failure of their first new drugs. Section 6.5 determines the common features of the latecomer firms' new-drug R&D patterns in view of exploratory learning. Section 6.6 summarises the chapter.

6.2 Market Position and Technological Level

This section briefly presents the market position and overall technological level achieved by the case firms, and then recalls a question that underlies this chapter.

Domestic market position

Most case firms have remained in the top ten in terms of sales size over the transitional period since 1987, after the introduction of the product patent system and the reform of NHI in 2000 (Table 6.1). Dong-a has maintained first place for more than 40 years, since 1967. Green Cross (GC) has grown based on biological products such as blood plasma and vaccines. As an affiliate of a *Chaebol*, LG Group, LG Life Sciences (LGLS) has been the most R&D-intensive pharmaceutical company until very recently. Hanmi rose rapidly to second position in 2006, from just around 15th in the 1990s, leading the generic drug boom in the 2000s. In contrast, two other case firms, Dongwha and Ilyang, have declined sharply to around 20th in the 2000s, from 4th and 5th, respectively, in the 1990s.[140]

Table 6.1: Case firms' sales ranking between 1985 and 2011

Companies	2011	2000	1985
Dong-a	1	1	1
Green Cross	2	3	5
Yuhan	4	6	6
Hanmi	5	7	18 (in 1995)
CKD	7	2	2
JW	8	5	8
LG Life Sciences	9	-	-
Dongwha	13	8	3
Ilyang	18	11	7

Source: Based on KPMA (2005)

Technological level achieved

All nine case firms have accumulated innovative (technological) capability to some degree by developing new drugs over the past two decades. Their technological level

[140] Other firms, Yuhan, CKD, Joongwae (JW), have stayed within the top ten sales companies over the period.

can be estimated approximately through the present pipelines of new drugs that they operate and their link to the global market.[141]

On the one hand, the case firms have levelled up the technological novelty of new drugs. All of the case firms (except Hanmi) have succeeded in licensing out their NCEs to Big Pharma, and have operated several pipelines of new molecular entities (NMEs), including both NCEs and biologics (Table 6.2). Factive by LGLS acquired an NDA from the US FDA in 2002. This makes Korea only the second non-Western country, after Japan, to succeed in acquiring an NDA from the US FDA for an NCE developed in-house; this reflects the attainment of a certain level of advanced technological capability.

Table 6.2: New-drug pipelines of case firms in 2012

Company	No. of NME pipelines	No. of out-licensed NMEs	No. of overseas clinical trials	No. of IMDs	Alliance with Big Pharma
Dong-a	20	3	4	2	GSK (share)
Green Cross	11	1	5	0	-
Yuhan	15	4	0	6	-
Hanmi	11	3 (DDS)	5	11	MSD (sales)
CKD	7	2	1	6	-
JW	5	1	1	10	Chugai (JV)
LGLS	17	8	3	0	-
Dongwha	8	3	0	0	-
Ilyang	2	3	1	2	-

Source: Author's elaboration from various data about the companies. NME: new molecular entities, including NCEs. DDS: drug delivery system. JV: joint venture

The case firms are now approaching the level of 'first-in-class' NCEs, beyond 'me-too' and 'me-better' NCEs (see Figure 3.4 for an explanation of the technological level of new drugs). For example, CKD, GC and JW are now conducting clinical development for first-in-class NCEs in the US. LGLS and Dongwha have licensed out first-in-class NCEs to the Big Pharmas (Gilead in 2007 and P&G in 2008), although their clinical development ceased in further clinical trials.

On the other hand, they have also maintained imitative drug development that falls at a level between generic drugs and NCEs in terms of technological level, such as incrementally modified drugs (IMDs or supergenerics) (Table 6.2), as they are a major source of market profits.

The relationship between technological achievement and market performance

[141] The case firms' technological effort, of course, has increased in parallel with the reinforcement of R&D personnel (Appendix 9).

One thing to note is that commercial performance of their technological effort seems to have stagnated in both the domestic and the global market. To begin with, their long-run new-drug R&D has been poorly compensated by the domestic market.[142] Only a handful of case firms have been successful commercially, such as Dong-a. Moreover, as of 2012, no case firm has succeeded in satisfactorily penetrating the markets in developed countries such as the US and the EU, with either its own new drugs or generic drugs.[143]

Herein, one question is raised about the gap between the firms' technological level and their (domestic and global) market position. As shown above, if one looks only at the technological dimension of the transition, they have reached a certain level of technology that has created at least a minimal level of innovation, such as developing NCEs and IMDs.

However, the question of why the KoPI is still struggling with commercial failure of new drugs remains unanswered. The following firm-level analysis focuses on answering the question through the following two chapters.

[142] For example, Yuhan (the second-biggest domestic company) and LGLS (the most R&D-intensive domestic company) have been stuck in a rut in their R&D pipelines due to a series of failures in the development stages. Others, such as Dongwha and Ilyang, have seen their market ranking for long-term innovative R&D considerably reduce.

[143] Essentially, most case firms intending to enter the global drug market focused only on technology export of their research outcomes (i.e., drug candidates), but this has proven largely unsuccessful. However, as a very recent phenomenon, the case firms seem to be making strenuous efforts to exploit the global market in a more strategic manner in terms of both export products and export regions. That is, they are now seeking to recoup their R&D investments from the global market. This movement has received additional impetus from recent change toward an unfriendly market environment for generic drugs in the KoPI. This has pushed the case firms to expand into overseas markets.

6.3 The First Round of New-drug R&D

This section examines the case firms' first round of new-drug R&D, which consists of the initial drug development projects and the later successful projects in which they developed their first NCEs.

The early projects are briefly discussed to present an overview of the difficulties the case firms faced as latecomers when they attempted new-drug R&D for the first time. New-drug projects of Dong-a are drawn upon, as this firm was the earliest domestic entrant to new-drug R&D; this is followed by aggregated supportive data from other case firms' projects (Sub-section 6.3.1). Next, the projects that produced the first marketed NCEs are analysed with regard to R&D process, strategy and marketing. As these were the first in-house developed drugs in these case firms, they had to go through the entire cycle of new-drug development, from drug discovery to approval and marketing (Sub-section 6.3.2).

Through this analysis, this section identifies the major challenges in conducting the exploratory mode of technological learning, and explores the possibility of overcoming those challenges.

6.3.1 Initial challenges to new drug development (after 1987)

Three NCE projects by Dong-a that failed to reach the market, and the overall failure of NCE projects by other case firms, are presented to analyse the barriers in exploratory learning that the latecomer firms faced in their first attempts at new-drug R&D (Sub-sections 6.3.1.1 and 6.3.1.2).

6.3.1.1 The case of Dong-a

Dong-a directed technological learning away from process development toward product innovation after 1987. Prior to 1987, Dong-a only focused on accumulating production capability in manufacturing generic drugs and APIs. The company then started to conduct new-drug R&D through focusing on chemical compounds (derivatives of known lead compounds) and phytomedicines (Table 6.3). In particular, the chemical compounds research was intended to develop “improved” NCEs in terms of efficacy and safety, rather than immediately trying to develop unknown lead compounds.

a. The first new drug projects focusing on upstream research

After the introduction of the product patent system in 1987, Dong-a launched a new project for developing NCEs. The company chose two clinical areas, the circulatory

system and antibiotics, based on their prior knowledge base of cardiac stimulation, antibiotics and anti-cancer drugs. In the former, Dong-a picked up ARB (angiotensin-II type beta blocker), which was of global interest at the time; ARB is a peptide responsible for the constriction of blood vessels and hypertension. However, the company ended the project once superior rival materials were presented (Interview 48 (K-Pharma)).

Table 6.3: Dong-a's patenting trends, broken into technological focal areas

R&D fields	1960s	1970s	by 1987	1988-1999
NCEs (derivatives and lead compounds)				13
Phytomedicine				4
IMDs (DDS, composition, structure)				9
Process development	3	10	21	26
Biotechnology				20
Total number of patents	3	10	21	72

Source: Author's elaboration from Korea patent office patent data.

Dong-a launched a research team to develop a carbapenem antibiotic (DA-1131) and an anthracycline anti-cancer drug (DA-125). Necessary prior knowledge bases for new-drug R&D, such as advanced synthetic technologies and screening skills, were accumulated through overseas training in the 1980s.[144] However, the two projects both failed in the preclinical and clinical stages. In particular, DA-125 was patented in 1990 and was believed to be the first commercial NCE developed in Korea. However, the development failed in the phase II clinical trial due to side effects and tolerability issues. The company finally gave up on the project in 2003.

b. Shift from upstream research to midstream research

> We have continuously failed in developing NCEs and thus, entering the 1990s, the R&D strategy for developing own drugs was switched away from the trial on screening and developing innovative lead compounds towards focusing on the further development of outsourced drug candidates. This outsourcing strategy was devised because we recognised a problem: upstream research was not able

[144] In the previous project for developing a phytomedicine in 1983 as their first new drug project, they were confronted with technological deficiency in testing and validating the effectiveness. To solve these technological problems, in 1985, Dong-a sent a researcher (Yung-moon Choi) to a Japanese pharmaceutical company, Otsuka, to train in HTS (high-throughput screening) technology for a year, and restarted the research the following year.

> to produce any commercial value at all. Then, we decided to focus on R&D that can directly create market profit (the CTO of Dong-a)

With realistic recognition of its limited research capability in the upstream stages, Dong-a tried to focus on the intermediate stages of validation research and the clinical development of the outsourced drug candidates, skipping the upstream research stage. Although new types of technological capability were needed for the intermediate stage (e.g., optimising the outsourced candidate materials, such as testing toxicity and drug-likeness, and preclinical-related technologies), the midstream technologies were relatively easier (tangible and definite) to master in a shorter time than those of drug discovery (Interviews 48 and 49 (K-Pharma)).

In the outsourcing strategy, one NCE pipeline was launched: a non-narcotic analgesic, DA-5018, originally developed by a GRI as a G-7 project by MOST. The preclinical and clinical development was conducted by Dong-a partly supported by MOHW for domestic clinical trials. At the same time, Dong-a also licensed out a drug candidate to Stiefel (now an affiliate of GSK) for multinational clinical trials in 1999. However, the project was ultimately dropped in the second clinical phase in 2006 due to toxicity issues.

All initial NCE projects that were launched in the late 1980s and early 1990s failed to reach the commercialisation stage due to an overall lack of technological capability in the upstream research and downstream development stages. Although there was a successful phytomedicine project, developing a phytomedicine does not require full upstream research capability due to the pre-existence of a natural plant as a drug candidate.

6.3.1.2 Learning by failure

Other case companies also embarked upon new-drug R&D for coping with the product patent system. By entering into new-drug R&D under the partial support of the NRDPs, case firms were able to accumulate initial stages of upstream research capability and distribute the risk of R&D investment to the upstream research (Interviews 45 and 52 (K-Pharma)). However, the initial projects, which were conducted between the late 1980s and 1990s, mostly failed to reach NDA (Table 6.4). From the viewpoint of technological capability building, two perspectives on the failed R&D projects can be pointed out.

On the one hand, these failures can be attributed to the absolute lack of competency (i.e., the amount of R&D resources) and technological capability across most stages of new-drug development, from upstream research (i.e., drug identification) to downstream development (i.e., clinical trials).

On the other hand, the initial trials to modify existing NCEs (i.e., the development of derivatives) and validate them pre-clinically allowed the latecomers to establish midstream research processes for new-drug development (Interview 42 (K-Pharma)). The midstream research processes was almost unnecessary in the previous production stage of copied drugs. As a result, learning by failure led to the accumulation of beginner-level innovative capability for further technological exploration.

Table 6.4: Trials to develop NCEs in the initial stage of new-drug R&D[145]

Case firms	Clinical indication of new-drug development	Projects launched (* : Support through NRDPs)	Result
Dong-a	· Circulatory system	· An ARB	·Failed
	· Antibiotics	· DA-1131*	·Failed
	· Anti-cancer	· DA-125*	·Failed
	· Analgesic	· DA-5018*	·Failed
Yuhan	· Liver disease	· YH-439*	· Failed
CKD	· AIDS	· CRB-405,	· Failed
	· Antibiotics	· CRB-529	· Failed
	· Anti-cancer	· CRB-401	· Failed
JW	· Antivirus	· NP-77A	· Failed
	· Arrhythmia	· KCB-328	· Failed
	· Anti Thrombin	· AT-1258 and AT-1340	· Failed
Ilyang	· Peripheral vascular	· BO-V-2*	· Failed
	· Anti-cancer	· KI-30606*	· Failed
	· Liver disease	· G009*	· Failed
Dongwha	· Antibiotics	· DW-116*	· Failed
	· Hepatitis B	· DW-471	· Failed
	· Anti-cancer	· DW-2282	· Failed

Source: Author's own elaboration from various data about the companies

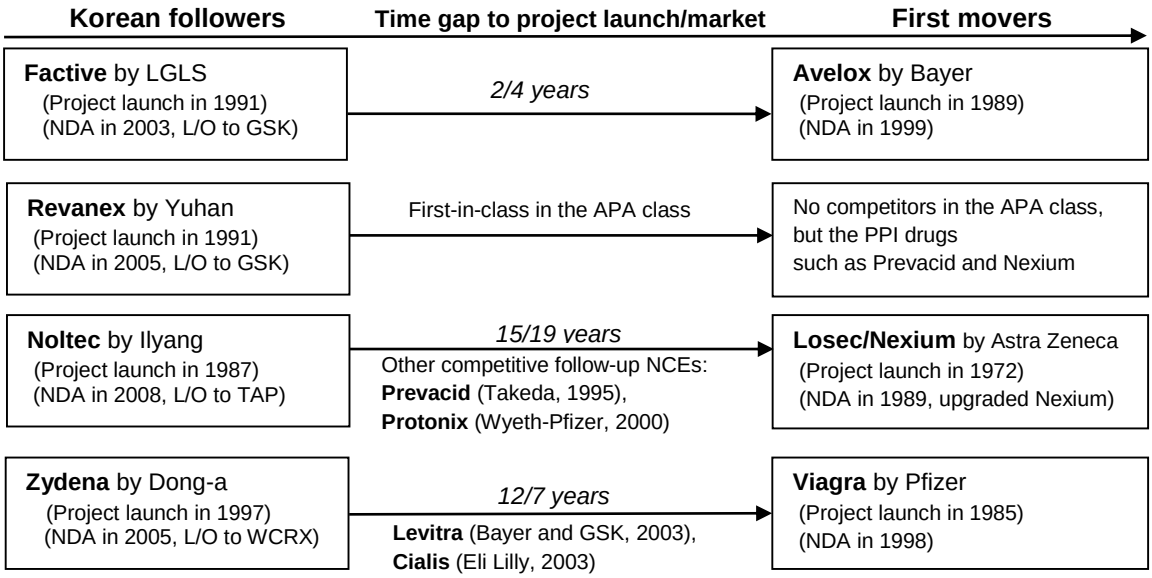
6.3.2 The first new drug - R&D process and strategy

After the series of failures of new-drug projects, the case firms, finally succeeded in developing their own NCEs for the first time. As noted, analysing the first successful projects helped identify the obstacles to latecomers' exploratory learning and the possibility of overcoming these obstacles, especially as the projects show the entire process of new-drug development, from drug discovery to commercialisation. The key barriers to understand are those faced by the case firms when, as latecomers, they rose to the challenge of new-drug development, a high-value market segment dominated by Big Pharma.

[145] Other firms - Hanmi: launched a new drug R&D project from the late 1990s, GC: biological products based company, LGLS: not identified as a research unit of LG Chemical in the 1990s.

In total, seven NCEs were developed by the case firms. Among them, four projects will be examined in this analysis: Factive (an antibiotic drug by LGLS), Revanex (an anti-gastric ulcer drug by Yuhan), Noltec (an anti-gastric ulcer drug by Ilyang) and Zydena (an erectile dysfunction drug by Dong-a). These projects were selected because they have some salient features of new-drug development and could therefore help characterise the challenges and possibilities of exploratory learning in the latecomer context.

Factive is the only NCE that acquired an NDA in the US before 2014, implying entry to the global market. Revanex is the only first-in-class NCE, although it competes with an established class of proton pump inhibitors (PPIs). Noltec was developed over the longest R&D period (21 years). Of these drugs, Zydena was the only successful drug in the domestic market. All four projects were started prior to the market launch of their rival first-in-class NCEs (Figure 6.1). They were all out-licensed to Big Pharma, aiming at the global market.



*TAP: Takeda-Abbott Pharmaceuticals in the US, WCRX: Warner Chilcott in the US, L/O: License-out

Figure 6.1: Catch-up pace between the first NCE and follow-up NCEs

Source: Author's own elaboration from various data about companies

To begin with, the first three projects, Factive, Revanex and Noltec, are presented as cases of commercial failure (Sub-sections 6.3.2.1, 6.3.2.2 and 6.3.2.3), whereas the fourth project, Zydena, was an exceptional case of commercial success (Sub-section 6.3.2.4). The following subsections identify common obstacles of the latecomer firms' exploratory learning, mainly by looking at the first three project cases. It also presents the possibility of overcoming these obstacles in the case of Zydena. Each project case

is described across the three phases of R&D: product strategy and drug discovery, clinical development including preclinical and clinical trials, and market penetration.

6.3.2.1 Commercial failure 1 – The first global-level drug: Factive by LG

Gemifloxacin (brand name: Factive), a recent generation (i.e., fourth generation) quinolone class antibiotic, has been referred to as the only Korean drug approved by the US FDA (as of 2012). Its NDA from the US FDA was acquired in 2003 after 13 years of R&D. However, global and domestic marketing of the drug largely failed (Interviews 33 and 36 (DBF)).[146] This case in particular reveals the barriers that must be overcome when a local latecomer firm takes up the challenge to develop a new drug targeting the global market (primarily the US and EU markets).

1) Product strategy and drug discovery

The Factive project was launched under the strategic focus on antibiotics. Antibiotics generally require continuous improvement due to drug resistance. Thus, in many cases the development of new antibiotics is attempted based on a known lead compound; and this implies less risk of cost and technology than the development of innovative NCEs.[147] Because of that, not only LGLS but also other case firms such as JW and Dongwha focused on antibiotics in the early 1990s.

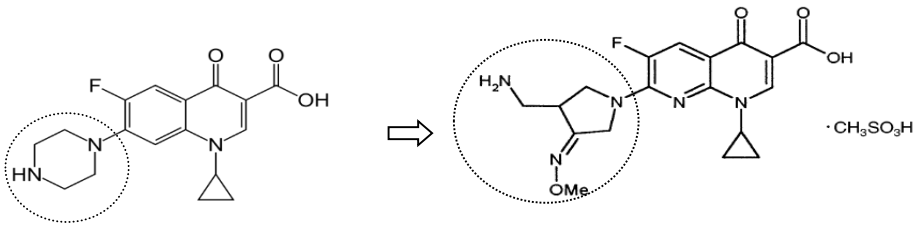


Figure 6.2: Ciprofloxacin (by Bayer) and its formula modification to Gemifloxacin (Factive)

Source: Left picture is from Wikipedia and right picture is from Hong (2001)

Derivation of the final drug candidate took four years. In the upstream stage, two research teams operated; this was the organisational set-up for competition and complementation, as it helped speed up drug identification (Lee and Kim 2001). The research teams were led by researchers scouted from outside, mostly in the US. One of

[146] Interviewees: the former heads of the new drug research centre of LGLS.
[147] Thus, it is easier to identify any commercial possibility in the early clinical trials (i.e., the ease of detecting side effects and efficacy and performing pharmacokinetic tests) compared with the other indications of disease. Comment: Dr In-chol Kim, the former CEO of LGLS (Medipharms Today, 9/4/2003).

them, Dr Hong, played a major role in deriving the final drug candidate.[148] The teams derived the drug candidate, LB20304a, by modifying the second generation of Ciprofloxacin in 1994 (Figure 6.2).

2) Clinical development

The preclinical trial was conducted overseas due to the deficiency of technological capability in middle-stage research for validation. After the clinical phase I trial in the UK, LGLS licensed out LB20304 to SmithKline Beecham (SB, now GSK) for co-development in 1997.[149] This decision was made for two reasons. One was the firm's limited capability to operate large-scale clinical trials as a latecomer firm inexperienced in multinational clinical development and suffering from financial insufficiency. The other was the time pressure of development against a competing project by Bayer, Moxifloxacin (brand name: Avelox, Avalox and Avelon), which was far ahead of LB20304a (Figure 6.1) (Interview 36 (DBF)).

SB carried out large-scale multinational clinical trials to cut down the drug's lead-time. Clinical trial phases II and III were consecutively conducted in 1,500 clinical centres in 40 countries involving more than 8,000 patients. Finally, in December 1999, SB filed an NDA with the US FDA. The full-scale commitment to development in such a short time, and the prompt NDA, showed that SB was desperately trying to overtake Bayer's competitive pipeline. Bayer's moxifloxacin was already approved by the US FDA in 1999 when SB completed its clinical trials.

While LG Chemical was certain of approval of its NDA, it was rejected by the US FDA in 2000 on the grounds of an imperfect toxicity study; the FDA demanded a more in-depth study.[150] As a result, SB renounced the reapplication of the NDA in April 2002, and returned all rights and clinical documents to LG Chemical.

From the perspective of SB, dropping the project allowed the company to avoid potential additional losses, which could have been enormous if it continued developing the drug, which had already cost around US$300 million.[151] In addition, SB had merged with Glaxo Wellcome, which had already experienced a suspension of marketing of its own

[148] See Lee and Kim (2001) for the explanation of drug identification in detail.
[149] LG Chemical exported LB20304a to SB with a US$37 million upfront payment and US$30 million of running guarantees for 20 years after its launch in 1997. The company also acquired the exclusive right to supply the API of Factive to SB.
[150] A rash had been expressed in 8% of fertile women in the clinical trial (Interview 36 (DBF)).
[151] SB input about US$300 million into the clinical trial phases II and III. LGLS invested approximately US$60 million for R&D, recording 29.4% of R&D intensity (R&D expenditure/total sales) in 2005 as the most R&D-intensive domestic pharmaceutical company.

quinolone antibiotic, Grepafloxacin (brand name: Raxar), in 1999 due to a series of toxicity accidents. In the end, GSK was sceptical of the possibility of successful marketing due to a few incumbent quinolone antibiotics already on the market (Interviews 33 and 36 (DBF)).

Therefore, the time had arrived for LG Chemical to decide whether to continue the project. For them, it was the first NCE they had put a lot of investment into, and they were confident of the technological superiority of the drug to the rival drug on the market (Interview 36 (DBF)).[152] In the end, they decided to continue the project by looking for a new overseas partner to complement the preclinical and clinical data, and to co-market after the NDA. Finally, in November 2002, LG Chemical entered into a contract with GeneSoft (now Oscient Pharmaceuticals, bankrupted in 2009), a biotechnology start-up in the US.[153] No better choice existed for LGLS because its NDA had failed once before and competing products were already popularised in the market (Interviews 33 and 36 (DBF)). This imposed practical constraints on partnering with another Big Pharma company.

3) Market penetration

LGLS and GeneSoft obtained approval as a Class 2 prescription medication in the US in April 2003.[154] However, the scope of indications was narrowed in the second attempt at NDA from four to two indications.[155] In the end, the scope-down of indications and approval for a Class 2 rather than a Class 1 drug led to severe restrictions on marketing activity and re-licensing out to Big Pharma (Interview 35 (DBF)).[156] Moreover, the drug had missed the most competitive time window (Interview 36 DBF)). As a result, its market performance remained under the expectations of LGLS, leading to the contraction of subsequent innovative R&D.

LGLS's present alternative strategy for marketing Factive appears to focus on the developing world, which is relatively easy to enter due to low levels of regulation. This makes local companies marketing easier. Globally, Factive has acquired approval in more than 28 countries. Interestingly, Factive was the top fluoroquinolone-class antibiotic

[152] At that time, an NDA of Factive from New Zealand was already under approval (December 2001).
[153] LGLS received US$40 million as a down payment and 14% share in GeneSoft. This meant that GeneSoft also anticipated the commercial success of Factive.
[154] AECB (acute bacterial exacerbations of chronic bronchitis) and CAP (community-acquired pneumonia).
[155] SB originally applied for approval for four indications in the first NDA application including ABS (acute bacterial sinusitis) and UTI (urinary tract infection).
[156] Factive was prescribed more than one million times, creating US$16 million in sales in the US in 2008. Oscient went bankrupt in 2009 and its promotion rights were transferred to several companies, depending on the region. A small pharmaceutical company specialising in respiratory system diseases, Cornerstone Therapeutics, started to market Factive in the US.

in Jordan in 2010, although the country's market is small in absolute terms. The drug was marketed in Jordan by Hikma, the largest pharmaceutical company in the country. This underscores the possibility of exploiting emerging markets for the sale of new drugs.

4) Summary

In conclusion, the case of Factive was the first full completion of new-drug R&D among Korean latecomer firms. In the process from local drug discovery to global marketing in the US, LGLS encountered a series of challenges. The first challenge was the company's weak upstream research capability to derive drug candidates. The second barrier was the absolute reliance on Big Pharma for global development, which caused a delay in further development. The last hurdle was the difficulty in penetrating both domestic and global markets due to the cumulative effect of the former two reasons and the domination of the targeted market by Big Pharma.

While LGLS finally reached the global marketing stage, overcoming the barriers in R&D, it was by virtue of the company's relative wealth as an affiliate of *Chaebol*. However, development success by no means always leads to marketing success. The following two cases more vividly reveal the difficulties that small latecomer firms commonly encounter in the three dimensions of new-drug R&D.

6.3.2.2 Commercial failure 2 – The most innovative drug: Revanex by Yuhan

Two further examples of new-drug development, Revanex by Yuhan (Sub-section 6.3.2.2) and Noltec by Ilyang (Sub-section 6.3.2.3), are analysed in this section with consideration of the replication logic (in case study) of the identified barriers, as well as in the complementary approach for identifying other barriers unrecognised in the Factive case.

1) Product strategy and drug discovery

The project to develop Revaprazan (YH-1885, brand name: Revanex) by Yuhan, an anti-gastric ulcer drug, was launched in 1991 and took 15 years of R&D, costing about US$40 million. Technologically, Revanex had a different lead compound structure as the existing drug Omeprazole, the first-in-class NCE in the active pump antagonist (APA) drug class (Figure 6.3). That is, it had a different mechanism of action from the H2 Receptor Antagonists (H2RA) and proton pump inhibitor (PPI) classes that had dominated the market for anti-gastric ulcer drugs.[157]

[157] Example of H2RA class drug: Zantac (API: Ranitidine, by GSK), PPI class drugs: Losec (Omeprazole, by Astra Zeneca) and Prevacid (Lansoprazole, by Takeda)

In spite of the risk of focusing on a novel target, Yuhan predicted a demand change to substitute-class drugs that could solve drug tolerance issues for H2RA drugs and had better efficacy than PPI drugs (Interview 47 (K-Pharma)). In 1995, the company's research team developed a candidate material, YH-1885, after four years of drug discovery.

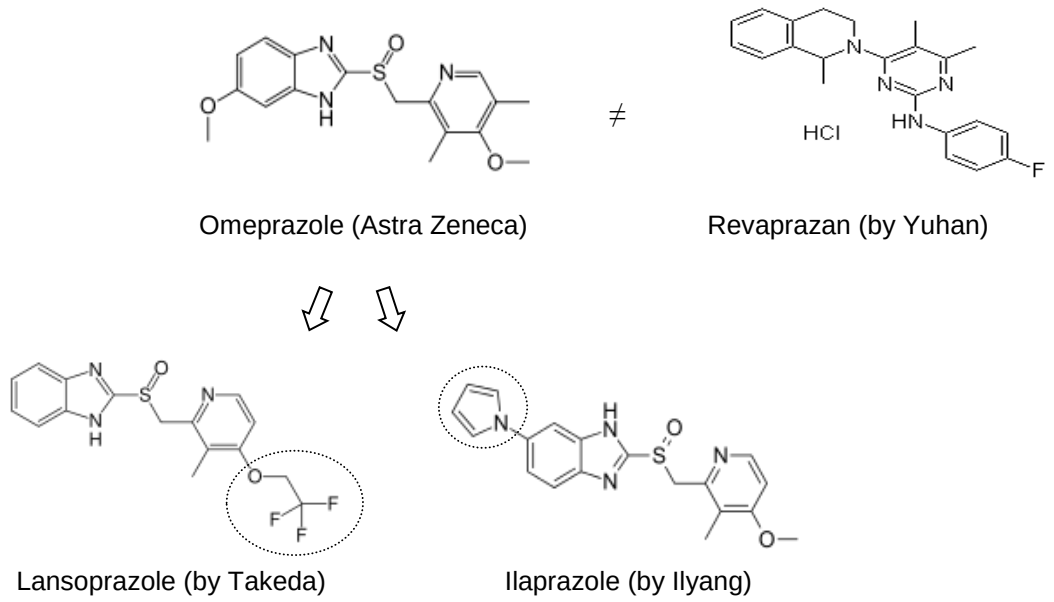


Figure 6.3 Structural formulae of Revaprazan (APA class) and other PPI drugs

Source: Wikipedia

2) Clinical development

After three years of preclinical trials and several failures, the drug candidate entered clinical trials in 1998. Yuhan out-licensed the compound to GSK in 2001 for global clinical trials and marketing.

However, the drug's clinical development was then suspended. GSK renounced clinical development in 2002 (just a month after renouncing LGLS's Factive). One reason for this was the low market potential of YH-1885 in the Western market after the merger of Glaxo Wellcome and Smith Kline Beecham in 2000, which saw the companies' R&D portfolios rearranged (Interview 47 (K-Pharma)). At the time, the Western market had much more market demand for drugs to treat gastroesophageal reflux disease (GERD) than gastric ulcers sparked by *Helicobacter pylori* (Money Today, 14/5/2002). The absorption rate of the compound presented another technological problem (Mirae Asset Report, 2002).

The renunciation by GSK again triggered scepticism about the project, and some suggested that it was just a waste of money and should be given up entirely (Dongallbo,

29/5/2005). However, the project was maintained after an alternative formulation was developed, resolving the problem with the absorption rate; Yuhan decided to market the drug domestically and acquired an NDA from the KFDA in 2005.[158]

3) Market penetration

However, in terms of market performance, Revanex only recouped its investment costs in 2010 after four long years of marketing, and its recent sales have been decreasing. Its stagnant market performance was due to changes in market trends and dominant drugs based on the PPI class. While the market for gastric ulcer treatment was larger when Yuhan started development, the GERD segment of the market now leads the domestic market. The segment for GERD had expanded to about 70% of the total gastric ulcer treatment drug market by 2011, but Yuhan did not respond by expanding the indications of the drug to GERD until later, in 2012 (EDaily, 10/10/2012). This indicates an organisational problem that inhibited the company from reflecting market dynamics in their new-drug R&D.[159]

While the drug's commercial performance lagged in the domestic market and global level development failed, efforts to penetrate the global market have been relatively successful in emerging markets, like with Factive. Revanex was out-licensed to both Chinese and Indian pharmaceutical companies: Zihzun in 2008 and ZydusCadila in 2009.

6.3.2.3 Commercial failure 3 – The longest R&D: Noltec by Ilyang

Ilaprazole (IY-81149, brand name: Noltec) by Ilyang followed a similar path and encountered the same difficulties as Revanex, revealing an even bumpier process of new-drug R&D. Ilyang launched the project to develop, a PPI-class gastric ulcer drug, with the aim of developing a best-in-class drug. The company acquired an NDA in Korea in 2008.[160] This drug had the longest development lead-time—21 years (1987 to 2008)—among the seven new drugs developed in the first round of R&D, at an estimated investment of about US$30 million. Meanwhile, the company fell to 20th place (in 2010) from around 3rd place (in the mid-1980s) in sales ranking, indicating that this very long-term new-drug R&D had caused the company severe difficulties.

[158] At the time, foreign pharmaceutical companies such as Sankyo and Astra Zeneca were still developing APA-class drugs in clinical trial stages I and II. CS-526 by Sankyo and Novartis, and AR-HO44277 by Astra Zeneca.
[159] In the interview and conferences, the lack of reflecting change in demand in the new-drug R&D was pointed out by the researcher of Yuhan, Dr Myung-ho Bae (Interview 46), and Dr Su-yeon Nam (the head of the R&D centre). The organisational problem will be seen in detail in the following chapter.
[160] Furthermore, this company acquired NDA in 2012 with their second NCE, Supect (API: Radotinib), for treating chronic myeloid leukaemia (CML), and were the first Asian developer of a CML drug to compete with a blockbuster drug, Glivec by Novartis.

1) Product strategy and drug discovery

Ilyang's research team originally started to develop an H2RA-class gastric ulcer drug, but it soon changed its development focus to PPI-class drugs in 1987. This was due to predictions of growth in the PPI-based gastric ulcer drug market. The H2RA-class drug market was shrinking in response to the emergence of PPI-class drugs such as Omeprazole (in 1989 by AstraZeneca), Lansoprazole (in 1995 by Takeda) and Pantoprazole (in 2000 by Wyeth-Ayerst Laboratories and Pfizer). Ilyang rightly seized a market opportunity by developing a me-better drug in this emerging PPI class.

However, the firm was faced with continuous failures in deriving drug candidates and did not succeed in developing Ilaprazole until 1996, as the 1,149th derivative, nine years from the project's start (the compound structure of the drug is shown in Figure 6.3). In the meantime, other modified NCEs, such as Lansoprazole and Pantoprazole, had already been launched on the market.

2) Clinical development

As the project targeted the global market from the start, Ilaprazole was transferred in 2005 to TAP, a joint venture between Takeda and Abbott Laboratories. TAP completed clinical trial phase II in 2007.[161] However, Takeda is also the original developer of the competing Lansoprazole.

Unexpectedly, Ilyang was faced with the renunciation of TAP prior to conducting clinical trial phase III in 2008. This was not because of any technological deficiency, but because of a strategic change by TAP (Daewoo-Securities 2010). TAP was a joint venture company that sold Lansoprazole in North America. The aim of in-licensing Ilyang's Ilaprazole was to substitute it for Lansoprazole, for which the product patent was about to expire (Pharmnews, 28/9/2008). Interestingly, TAP was also developing an in-house candidate as a substitute for Lansoprazole, TAK-390MR (Doctor's News, 24/3/2008).

In 2008, Takeda fully took over TAP. As a result, Ilaprazole was downgraded to a backup material for Takeda's own TAK-390 in case of negative results during clinical development. From the perspective of Ilyang, it would have been better if the rights to Ilaprazole had been taken by Abbott Laboratories, as Abbott had no PPI drugs.

Hence, Ilyang was faced with the decision to either continue the project or drop it. As the company chose to continue, Ilyang was left looking for a Big Pharma to complete clinical

[161] Takeda Pharmaceuticals: the largest pharmaceutical company in Japan, the original developer of Lansoprazole

trial phase III in the US. For them, dropping the project due to external reasons was a difficult decision because they had bet on the NCE overcoming 20 years of financial deficiency.

3) Market penetration

While the drug was launched in the domestic market in late 2009, it showed a sluggish market performance, recording only about US$2 million in 2010.[162] As with Revanex, the company also missed the chance to market it for GERD from the start, and only completed clinical trials for expanding the indications to GERD in 2012. However, Noltec has found better marketing contracts in emerging markets such as China (Livzon in 2002) and India (Merck KGaA in 2009), as in previous cases.

4) Summary

On the whole, the cases of Revanex and Noltec met with similar difficulties. First, independent pharmaceutical firms, unlike LGLS, struggled with weak upstream research capability due to insufficiently experienced researchers and finances that undermined the acceleration of drug discovery. Second, absolute reliance on Big Pharma delayed the overall development lead time. Big Pharma's renunciation of clinical development damaged both drugs' credibility and made it more difficult to transfer them to another Big Pharma. Again unlike LGLS, Yuhan and Ilyang were not able to continue global development on their own as small, independent firms. Third, their R&D process failed to properly respond to changing market needs. When the new drugs were first launched in the domestic market, major demand had already changed to another indication. The companies belatedly conducted additional clinical trials to deal with this indication, rather than engaging in simultaneous clinical development.

6.3.2.4 Commercial success – Drug for local & niche: Zydena by Dong-a

In contrast to the previous cases, Zydena was an exceptional commercial success immediately after its market launch. This section compares this drug's success with the previous cases of commercial failure in order to identify the factors that can overcome the latecomers' obstacles identified above.

1) Product strategy and drug discovery

In the late 1990s, Dong-a again attempted to develop an NCE through its own upstream research for drug discovery. This was based on internal confidence about drug discovery

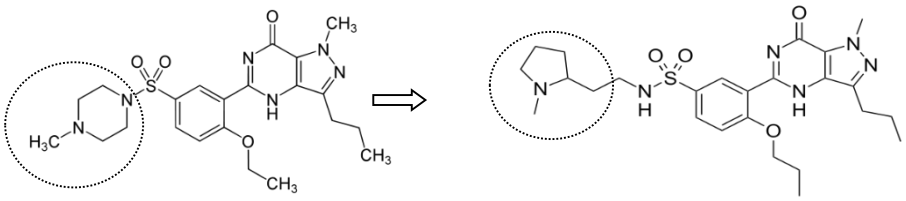
[162] Interestingly, the sales of Noltec have rapidly increased since 2013 after the expansion of the indication to GERD. This implies the importance of the R&D strategy that reflects the market dynamics from the start of product conception and drug research.

based on technological accumulation in midstream research of outsourced drug candidates through previous projects (Interview 49 (K-Pharma)).

In line with this, Dong-a aimed at improving a first-in-class NCE that was being developed by other firms, hoping that this could create a new market of indications in the near future. The benchmarked first-in-class NCE was within the technological scope that Dong-a had previously accumulated and experienced. This development strategy is similar to that of LGLS and Ilyang, that is, the 'me-better' strategy. However, Dong-a was more agile in its shift from the initial target market to a less competitive niche market.

The Zydena project was inspired by the mechanism of action of Viagra (compound: Sildenafil), the drug for erectile dysfunction (ED) developed by Pfizer, and its close relevance to Dong-a's prior knowledge base about cardiovascular disease.[163] Dong-a had previously accumulated extensive knowledge of cardiovascular disease during the ARB project in the late 1980s, even though that project failed.

Prior to the approval of Viagra (launched in 1998), Dong-a started to develop a modified NCE based on the lead compound of Viagra under the strong initiative of the company's owner, Dr Shin-ho Kang. In 1999, the research team derived a drug candidate, DA-8159 (Udenafil), a novel phosphodiesterase5 (PDE5) inhibitor (Figure 6.4). It just took two years to derive this drug candidate based on a prior knowledge base and simultaneous work by the functional team (meaning that synthesis of derivatives, screening of efficacy and pharmacokinetic research and toxicological tests could occur at the same time).



Viagra (Sildenafil) Zydena (Udenafil)

Figure 6.4: Modification of the first-in-class NCE of Viagra to Zydena

Source: Wikipedia

2) Clinical development

Dong-a completed a phase I clinical trial in the UK in 2002. Under partial funding from the MOHW, Dong-a completed domestic clinical trials and then acquired an NDA from the KFDA in 2005. As a result, Zydena became the fourth PDE5 inhibitor for the erectile

[163] Viagra was originally intended to treat angina pectoris, until its efficacy for overcoming ED was probed in clinical trials in 1994 (for angina pectoris).

dysfunction market, following Viagra (Pfizer, 1998), Levitra (Bayer and GSK, 2003) and Cialis (Eli Lilly, 2003).[164] It should be noted that this project prioritised domestic development over global clinical development.

3) Market penetration

The unusually rapid development of Zydena was successfully converted to good performance in the domestic market and the export market to developing countries. The drug has recorded about a 30% domestic market share in the erectile dysfunction market, behind only Viagra, with about US$25 million in sales in 2011. Dong-a is also conducting further clinical trials to expand its scope of prescription to indications such as pulmonary hypertension.

Global marketing remains a challenge; Zydena is now in the approval process in the US and at the start of marketing in Brazil. Warner Chilcott (specialising in dermatology and urology) licensed the drug from Dong-a, and the phase III clinical trial was completed in the US in 2013. Interestingly, the product right to Zydena was returned to Dong-a in 2014 after the merger of Warner Chilcott with Actavis, the largest US generic drug producer. Zydena is now being prepared for an NDA.

4) Summary

On the whole, Dong-a's first NCE, Zydena, has found extraordinary commercial success. This success was driven by the fact that the company's approach was different from the previous three firms in coping with the obstacles facing latecomers to new-drug R&D.

First, Dong-a also had weak upstream research, in particular in drug discovery, and few resources. While Dong-a adopted a 'me-better' strategy to overcome this difficulty, like the other case firms, the company targeted its market better than the other firms. It strategically searched for a niche market that could utilise its prior knowledge accumulation, rather than sticking to major markets. Dong-a attempted to develop an improved NCE of Viagra, which was in the clinical development stage, at a time when the erectile dysfunction market was still emerging. By virtue of its prior knowledge base, such as a chemical library built through previous failed projects, Dong-a succeeded in developing an NCE within two years. In contrast, the other three drugs examined took longer to develop and were developed for a competitive major market, making it easier to miss the changing market needs and lowering commercial potential.

[164] The technological competitiveness of Zydena is based on its faster and longer-acting efficacy compared to Cialis and its reduced side effects compared to Viagra.

Second, Dong-a intentionally prioritised the domestic market, while other firms aimed at global development through partnerships with Big Pharma. By focusing on the domestic market, the company was able to lessen the lead time of clinical development and product approval. Early entry is particularly important for me-better NCEs because the first-in-class NCE and the earliest me-better NCEs achieve a stronger market position than follow-on NCEs who enter later. While Dong-a was able to take a strong market share through its domestic-first strategy, which meant that it was competing with only a few drugs, the market entry of the other three firms' NCEs was considerably delayed by the failure of global development. These three cases showed that success in global development depends not only on technological superiority, but also on the competitive environment surrounding Big Pharma. These cases demonstrate the difficulty for latecomers entering an advanced market with weak capability for dealing with Big Pharma and overseas regulatory frameworks.

Overall, on the one hand, the case of Dong-a shows that there is a possibility for Korean latecomer firms to do well in the new-drug business by taking alternative routes to success. On the other hand, the other three cases show that there are many common obstacles that latecomer firms face in new-drug R&D and market entry. The following section shows how Korean latecomers have tried to overcome the obstacles that they faced in the first round of new-drug development.

6.4 The Second Round of New-drug R&D

This section discusses how Korean firms reconfigured new-drug R&D in the 2000s as a direct response to the commercial failure of the case firms' first in-house-developed NCEs. This reconfiguration was also influenced by the changing institutional and technological environment, such as the growth of the ETC drug market after NHI reform, the growing threat from Big Pharma under the FTAs with the US and the EU, and the deepening influence of biotechnology. With firms under increasing pressure from these changes, intensive involvement in innovative R&D became seen as the only way for survival if they did not want to continue to be generic drug producers.

The reconfiguration of new-drug R&D occurred through the diversification of the paths of new-drug development. This section describes these new paths by presenting the case of a specific firm that adopted each path, then presenting other firms' cases at an aggregated level.[165] By doing so, this section explains how the case firms have

[165] Note that the diversification does not indicate the differentiating trajectories of innovative R&D across case firms; it represents the overall expansion of the scope of innovative R&D in each single case firm.

reconfigured the overall pattern of the exploratory mode of technological learning in new-drug R&D.

First, the synthetic drug development that was the main focus in the previous round of new-drug R&D was diversified in two ways: through a focus on incrementally modified drugs (IMDs) based on process innovation (Sub-section 6.4.1), and by redirecting NCE development to less competitive niche markets (Sub-section 6.4.2). Moreover, diversification into non-synthetic drugs occurred through two routes: the rush to phytomedicines (Sub-section 6.4.3), and the refocus on biological drugs including biologics and vaccines (Sub-section 6.4.4).

6.4.1 Process innovation - Incrementally modified drugs

Development of IMDs is one alternative path to the singular concentration on the development of NCEs. This path is technologically driven by upgrading the process technologies that were accumulated from previous imitation stages. IMDs are often based on developing new drug delivery systems (DDSs).

Under the enforcement of SPD in 2000, domestic pharmaceutical companies were forced to rapidly shift their development focus to the ETC market. The case firms immediately responded by launching the first generic drugs. The focus on the first generics was driven by a favourable drug pricing policy, which priced them at 87% of the price of the original drug (until 2008).

This first generics strategy, which hinged on making minor modifications to a drug, such as changing a base in the original compound, evolved into the development of more novel IMDs, such as combination drugs and application of new DDSs. In doing so, innovative capability could be incrementally accumulated. The following example shows the successful adoption of an IMD-based incremental innovation path.

1) The case of Hanmi as the first entrant into the IMD market[166]

Domestic pharmaceutical companies crowded into the generics market to survive NHI reform. This resulted in intense competition within a few popular therapeutic areas. Hanmi launched 120 generic drugs between 2000 and 2009, the most of any domestic company. In particular, Hanmi focused on launching first generics with differentiated

[166] Interview 44 (K-Pharma).

process technologies at formulation to evade patent barriers accumulated in the 1990s.[167] As a consequence, Hanmi has dominated the generic market since 2000.

On the basis of the strong imitative technological capability, Hanmi started to take on exploratory learning by focusing on its own DDSs, using them as platform technologies that could then be used to develop more innovative drugs.[168] In 2004, Hanmi launched Amodipin, a modification of Pfizer's anti-hypertensive drug Norvasc (API: Amlodipine), a calcium channel blocker (CCB). At that time, Novarsc monopolised the domestic market. As the original API, Amlodipine, was unstable in oral administration, Norvasc was formulated by attaching a besylate salt to improve stability and absorption rate. While the scope of patent rights of Amlodipine besylate (Norvasc) was due to expire in 2010, that of Amlodipine itself had already expired in 2003.

Hanmi tried to break the original patent of Amlodipine besylate by developing an alternative salt. The company succeeded in developing camsylate (an alternative salt) and attached it to Amlodipine in 2004, improving the drug's stability and absorption rate.[169] The modified drug, Amodipin, overtook Norvasc in terms of sales size, recording US$195 million in cumulative sales in the local market by 2009.

Moving forward, the incremental IMD strategy of changing new salts and single isomers evolved into a more active IMD strategy that focuses on developing new administration routes and new combinations of existing APIs. In 2009, Hanmi launched a new combination drug, Amosartan, a combined version of Amodipin and Losartan (ARB: angiotensin receptor blocker, Brand name: Cozaar by Merck), an anti-hypertensive and analgesic, respectively. As Amosartan was a new combination of two APIs, it was required to undergo a full clinical trial as with NCEs, whereas the previous IMD, Amodipin, underwent only selective and small-scale clinical trial phases I and III.[170] Amosartan was the second therapeutic combination IMD, after Exforge by Novartis (in 2007). The

[167] Several Big Pharmas filed lawsuits against Hanmi alleging patent infringement about manufacturing and formulation in 1984 (by Hoechst, now Sanofi-Aventis about Claforan), 1987 (by Roche about Ceftriaxone), and 1990 (by AstraZeneca about manufacturing omeprazole). In particular, Hanmi won the lawsuit against Roche through proving the novelty of the synthetic pathway and then Roche conversely suggested the technological transfer of Hanmi's new synthetic pathway in 1989. It was the first technological export (a manufacturing process patent) by the domestic pharmaceutical company, recording US$6 million as the fixed royalty.

[168] The focus on DDSs was based on their technological strength in synthesis and formulation process technologies previously accumulated for imitative production.

[169] This salt-changing strategy has not only been a local phenomenon, but has also occurred in the US. The patent conflict between Pfizer and India's Dr Reddy about Novarsc show a similar story.

[170] That is, technologically it was a more complex and explorative type than new salt-based IMDs, demanding firm proof of safety and efficacy, although it was a combination of the two pre-existing APIs.

development of Amosartan demonstrates the technological capability of Hanmi to develop more advanced IMDs.

Through the incremental innovation process, a series of new DDSs has been developed, such as an integrated controlled release system for longer or more immediate efficacy. Hanmi finally established two key DDSs as its core platform technologies in the late 2000s: Orascovery for chemical drugs and Lapscovery for biodrugs. These undergird the company's on-going IMD and NME pipelines.

2) Dual perspectives on incremental innovation through IMDs

Hanmi's incremental innovation reveals two perspectives on latecomers' exploratory learning. In the positive view, the company used this technological path as a 'technological bridge' between imitative development and more exploratory R&D; this was assumed to be the most suitable R&D strategy for small Korean pharmaceutical companies. From an external point of view, it was seen as the most technologically adaptive strategy for the increasing ETC market, as drug pricing policy was favourable to generic drugs (Interview 39 (K-Pharma)).

In addition, incremental innovation gave companies the potential to acquire a global marketing channel through Big Pharma. This 'stepwise' technological upgrade was the KoPI's first real opportunity to catch up with the global market. In 2009, Merck was contracted to co-market Amosartan in six Asia-Pacific countries under the brand name Cozaar XQ. In 2011, the contract was then expanded to 30 countries, including the EU market (estimated to be around US$2 billion over 10 years). With the increasing global competition in the hypertensive drugs market, Merck was being forced to strengthen its original product, Losartan, against the rival combination drugs Exforge by Novartis and Pfizer, and Sevikar by Daiichi Sankyo.

However, there are also critics of this incremental approach. One leading researcher at a case firm, who once worked for a Big Pharma company in the US, noted that the approval of IMDs had distorted the pattern of new-drug R&D by domestic companies, leading to the conception that this was simply a way to evade patents (Interview 51 (K-Pharma)). He argued that focusing on minor modifications prevented companies from becoming fully involved in 'real' new-drug R&D. In fact, the initial pattern of 'minor' modification of the base has become so common among domestic companies that the NHI now denies salt-changed super-generics as a form of new IMD; they are regarded as no more than a generic drug.

Nonetheless, the incremental strategy has provided real market profits for short-term survival and organisational slack for further new-drug R&D. Indeed, Hanmi finally succeeded in reaching the innovation stage of developing a first-in-class drug. The company licensed out two first-in-class drug candidates, HM71224 and HM61713, an oral Bruton's tyrosine kinase (BTK) inhibitor to Eli Lilly and a 3rd generation epidermal growth factor receptor (EGFR) targeting agent to Boehringer Ingelheim in 2014. Both drugs are licensed out with an initial royalty of US$50 million, and a potential maximum royalty of more than US$600 million, depending on development and sales performance.

3) Other case firms in the IMD-based R&D path

Other case firms, and most domestic firms seeking R&D, have engaged in similar R&D activities in IMDs and DDSs. Most case firms are now operating IMD pipelines (Table 6.2), and by 2011, 200 IMD pipelines were being operated by 30 domestic companies (KDRA 2013).[171] Of the 200 pipelines, 111 were being conducted to improve formulations (i.e., DDS related) or develop combination drugs, while 15 pipelines were involved in minor modification in the structure of original compounds.

As pointed out earlier, the IMD path based on incremental innovation is widely regarded as the most realistic strategy for latecomer firms. This is based on the close technological relationship between the prior knowledge base of the synthetic and the formulation technologies used to efficiently copy the original drug. This initial exploratory learning showed high market profitability, at least within the short term. Incremental innovation is also the same path used by other major Korean catch-up industries. Overall, the entry of firms into innovation through IMDs has proceeded relatively smoothly until now, compared with the following emerging paths.

6.4.2 Product innovation – Quality-of-life drugs

The shift to ‘quality-of-life’ (QOL)-related market segments was identified as another path of new-drug R&D that would help firms emerge from a single focus on antibiotics/anti-cancer drugs and other major market segments. QOL drugs treat lifestyle-related diseases, as opposed to necessary drugs such as antibiotics. This new direction was a strategic response to the commercial failure of the case firms’ first new drugs, which were largely antibiotics and anti-cancer drugs. In the search for a profitable NCE, for example, metabolic, cardiovascular and urinary diseases have received new attention

[171] By 2008, 92 pipelines of IMDs were operated by 22 of the 35 domestic companies, including all of the case firms (KDRA 2009).

(Table 6.5). The case of LGLS shows the redirection of R&D focus and the underlying difficulties that face latecomers seeking to develop commercially viable new drugs.

Table 6.5: The NCE pipelines of non-antibiotic and anti-cancer in 2012

Case firms	Pipelines in QOL	Anti-cancer/ antibiotics	Indications in the QOL pipelines (No. of pipelines)
Dong-a	8	1	Diabetes (1), Erectile dysfunction (1), Gastritis/dry eye (1), Hypertension (3), IBS* (1), Premature ejaculation (1),
Yuhan	8	2	Allergic Rhinitis (1), Atherosclerosis (1), Degenerative Disc (1), GERD* (1), IBS (1), Osteo Arthritis (1), Diabetes (2),
Hanmi	0	5	-
CKD	3	2	Diabetes (1), Lipidosis (1), Obesity (1)
JW	3	2	Arrhythmia (1), Gout (1), Osteoporosis (1)
Green Cross	1	2	Parkinson's Disease (1)
LGLS	9	1	Atherothrombosis (1), Diabetes (3), Gout (1), Hypertension (1), Liver fibrosis (1), Obesity (1), Prokinetic (1)
Ilyang	1	2	Leukaemia (1)
Dong-wha	2	2	Cerebral Apoplexy (1), Osteoporosis (1)

* IBS: irritable bowel syndrome, GERD: gastroesophageal reflux disease

1) Redirection of the development of NCEs by LG Life Sciences

The pharmaceutical business unit of LG Chemical was spun off due to the expectation of successfully marketing their first NCE, Factive, in 2002. However, the global marketing failure put pressure on the newly established company, LGLS, to restructure its R&D portfolio for more profit-creating drug development. [172] One of the most noticeable changes was the rearrangement of the company's R&D pipelines, which had once focused on antibiotics and anti-cancer drugs, to focus on QOL drugs for metabolic, cardiovascular and neural systems. The latter market segments were estimated to have less competition than the former. This strategic change has brought both positive and negative effects to the company's new-drug R&D.

On one hand, LGLS has seemed to succeed in developing drugs that are commercially more prominent. In 2012, the company launched its second NCE for the diabetic market, Zemiglo, and the drug was also licensed out to Sanofi Aventis for export to emerging markets in 2012. Its sales reached about US$ 13 million in 2014, and it is regarded as a domestic blockbuster.

[172] Behind the sudden change, LGLS was pushed by the holding company, LG, to show managerial performance as an independent company; LG demanded a change in its tendency to be an R&D institute sheltering behind a Chaebol (Interview 35 (DBF)). In the end, LGLS's choice was to promote the development of generic drugs, which could guarantee a short-term profit.

However, the redirection of the R&D focus resulted in a hole in the NCE pipelines for a considerable period and the loss of experienced researchers in the late 2000s. As of 2014, there was only one NCE pipeline in the clinical stage, while other two remain in the drug discovery. Moreover, about 200 researchers concentrating on antibacterial and anti-cancer drugs were dispersed across the new QOL research areas, and many of them left the institute to continue their research topics elsewhere.[173] Although the company, as an affiliate of *Chaebol,* has gradually recovered its loss in R&D personnel*,* it is clear that this strategic conversion weakened the technological capability that had been accumulated over 15 years of exploratory learning.

2) Other case firms redirecting NCE development

Returning to the main point, the shift in LGLS's focus to QOL drugs is supported by the experience of two other case firms, Dong-a and Yuhan. For example, one of Dong-a's most recent projects in clinical trials is an anti-diabetic compound to treat Type 2 diabetes (DA-1229). Dong-a focused on deriving a superior alternative compound to Sitagliptin, a dipeptidyl peptidase 4 (DPP-4) inhibitor, which was launched by Merck (brand name: Januvia) in 2007, following the same strategy as its previously successful project of Zydena, that is, a me-better strategy in the QOL area.

There are two main reasons why Dong-a continues to focus on the me-better strategy rather than the first-in-class strategy. First, the company has still relatively few resources to devote to upstream research on identifying new targets and lead compounds. Additionally, Dong-a has shown relatively strong middle-stage R&D capability, concentrating on the modification of existing lead compounds like Zydena.

Indeed, based on internal midstream R&D capability, Dong-a seems to be aiming to be a specialised developer in a few QOL market segments by taking advantage of external opportunity from Big Pharma's tendency to outsource drug candidates. The CTO of Dong-a argued that, for a late-mover firm, it was most effective to place R&D focus on middle-stage development within a few niche markets:

> "We aim to become an innovator in disease areas that the Big Pharmas are not eligible to directly enter because of the market size, i.e., niche markets. The QOL-based niche market will allow a small-sized, late entrant to acquire more market opportunity than intensely competitive antibiotics. We will quickly develop better, best, or innovative NCEs in these areas and complete clinical trials by the phase

[173] For example, some involved in antibody research moved to KRIBB and others set up DBFs to continue their own research (e.g., LegoChem Bioscience). According to an interviewee, almost 100 researchers left the company.

IIA stage, minimising the R&D period. Then we will transfer [the drugs] to Big Pharma for multinational development (2A model). Through this strategy, we will grow as a specialised innovator in a few therapeutic areas."

Other case firms also diversified their NCE pipelines from necessary drugs to QOL drugs, although their switchover was not as radical as that of LGLS and Dong-a (Table 6.5). By 2012, QOL drugs accounted for 77% of all 238 pipelines (by 35 R&D intensive firms), up from 64% of 89 NCE pipelines by 32 R&D intensive firms in 2008 (KDRA 2009, 2013).[174] In 2012, among all 238 pipelines by 35 R&D-intensive firms, there were only 55 pipelines dedicated to anti-cancer drugs and antibiotics. Overall, the redirection of NCE development towards QOL drugs reflects firms' search for innovation paths with more commercial potential, especially given competitive pressure from Big Pharma in the major market segments.

6.4.3 Production innovation - Phytomedicines

Phytomedicine R&D is another important path of diversification (Table 6.6). It is based on the local knowledge base of traditional Korean medicine. The exceptional commercial success of a phytomedicine developed in early 2000 ignited the phytomedicine R&D expansion of the 2000s.[175] Five of the nine case firms have operated nine phytomedicine pipelines. Furthermore, 64 phytomedicine pipelines by domestic companies are estimated to be in clinical trials (Popular Science, 24/12/2010).

Table 6.6: KFDA approval of phytomedicine clinical trials

	2004	2005	2006	2007	2008	2009	2010
Phase I				1		1	
Phase II	1	1	6	6	4	7	8
Phase III			1		3	5	4
Total	1	1	7	7	7	13	12

Source: KDRA (2009)

1) Motive for the rush to phytomedicine R&D

The phytomedicine Stillen, an anti-gastritis agent (DA-9601, eupatilin), became a best-seller in the 2000s. It was first outsourced by a university research team in 1994 under

[174] However, it should be noted that the total pipelines of 238 consists of not only NCEs but also other types of new-drugs: NCEs – 112, Biological drugs – 71, Phytomedicines – 55.

[175] Shinbaro by Green Cross for osteoarthritis, Motilitone by Dong-a for functional gastrointestinal disorders, Synatura by Ahn-kook for cough and congestion, Layla by Viromed for osteoarthritis in 2011. After only a year, Synatura and Motilitone recorded sales of approximately US$35 million, US$10 million in 2012. In particular, Synatura was licensed out to Gravity Bio, a US-based specialised pharmaceutical company to cough, cold and allergies, in 2013.

pressure to develop new drugs. The drug candidate entered clinical development partially supported by a NRDP from the MOHW in 1995 and then was approved by the KFDA in 2002. Stillen is the most prescribed ETC drug in 2012, reaching about US$ 90 million in sales. The drug's remarkable commercial success compared with NCEs attracted other domestic firms to phytomedicine development in the second round of new-drug R&D.

In general, phytomedicine R&D costs less (Table 6.7), and the concept of the drug is easier to substantiate, compared with the development of NCEs. Moreover, efficacy is largely already known through the use of corresponding herbal plants throughout generations.

Table 6.7: Comparisons between NCEs and phytomedicines[176]

R&D stages	R&D Cost (millions of $)		Development lead time (months)	
	NCE	Phytomedicines	NCE	Phytomedicines
Drug discovery/ Pre-clinical trials	90	2-3	33.5	36-60
Clinical trial 1	48	0.2	15.5	Exemption to 12
Clinical trial 2	54	0.5-1	24.3	14
Clinical trial 3	36	3-5	30.3	24
NDA	6	0.3	30.3	18
Total	234	5.9-9.5	11 years	7 to 10 years

Source: Cho (2003)

These technological and cost advantages compared with NCE development are essentially based on the profound knowledge base of traditional Korean medicine. Koreans have accumulated a large body of knowledge about herbal drugs and clinical practice, although this knowledge has been largely unexploited by modern science. As the CTO of Dong-a put it, this makes it "relatively easier to generate a research idea from the existing traditional materials as sources of new drugs. Because we can utilise this information and knowhow, the R&D costs and time are reduced compared with developing NCEs. Moreover, the possibility of market success is higher because of the lower psychological barrier to herbal materials."

[176] This data, in fact, is a rather incorrect comparison using different criterion. In the case of NCE, it seems to refer to the drug development at the global level, i.e., by the Big Pharma, while the phytomedicine data seems to be based on the company's internal costs. According to the KDRA data, NCE's domestic development to date constituted about US$23 million, while that of phytomedicine constituted around US$17 million on average.

Specifically, the development of phytomedicine drugs based on traditional medicine offers two technological advantages that can help overcome the most critical barriers to latecomers. First, upstream research for the identification of target and lead compounds is unnecessary. Scientific extraction and validation of the existing materials can replace the key steps of upstream research. Second, the clinical development success rate is higher due to prior knowledge about efficacy and safety based on traditional medicine. Although standardisation of the raw materials remains a challenge, this is an easier task than drug discovery research. Thus, for most domestic firms with weak upstream research and financial capability, the development of phytomedicine is a solution to overcoming R&D barriers.

Moreover, the government has supported phytomedicine development. Unlike NCE development, traditional medicine-based phytomedicine development has received direct policy attention since the mid-1990s, when the NRDP for Korean new-drug development was launched. In 2000, the government established a promotion act for phytomedicine development that exempted phytomedicines from initial safety and efficacy tests as long as they were being developed for the indications referred to in the officially acknowledged 12 books of traditional medicine.

On the whole, the recent rush to phytomedicine R&D has the same cause as the focus on IMDs (and DDS) and QOL-oriented NCEs: Firms needed to find alternative routes of exploratory learning to realise profits amid technological uncertainty. In particular, the innovation path for phytomedicines can be seen as the outcome of both firms' active participation and direct governmental support for R&D and regulation.

6.4.4 Product innovation – Biological drugs

Biotechnology R&D, ranging from imitative development to innovation trials, has long been one of the most promising alternative paths for pharmaceutical companies. In fact, the attention to biotechnology by case firms was a relatively less novel phenomenon than their focus on QOL drugs and phytomedicine. Rather, biotechnology R&D can be said to have been occurring across the entire transitional period of the KoPI, in parallel with NCE development trials. Biotechnology was once regarded as an alternative business opportunity that could lift a company up to the level of innovator in the early 1990s, at least by a few case firms. To date, however, these firms have still remained at an imitative learning stage.

The recent refocus on biotechnology R&D can be attributed to the joint effects of the national ambition for biotechnology and the firms' search for new business opportunities.

Under a regime of active governmental support to biotechnology, ranging from biosimilars and new biologics to stem cells, vaccines and bioinformatics, case firms have continued biotechnology research, with a recent refocus on commercialisation.

1) Early entry into biotechnology, but passive expansion to commercialisation

For example, Dong-a has shown continuous R&D investment in the emerging biotechnology field since the 1980s, although its market performance is still opaque. The company has paid no less attention to biotechnology than to synthetic drug R&D, in terms of entry time and persistence (Table 6.8). Dong-a has conducted biotechnology research for about 25 years and now maintains about 80 researchers focusing on biotechnology, accounting for almost 30% of its entire research staff. In spite of this long-term investment, the biotechnology business has only just started to contribute to the company's revenue, comprising about 15% of total sales entering into the middle of the 2000s, mainly from imitative protein drugs, i.e., biosimilars.

Table 6.8: Dong-a's R&D achievements in biotechnology

Year	Biological drugs	Chemical drugs
1980s	· Hepatitis B virus (HBV) diagnostic agent in 1986 · AIDS diagnostic agent in 1988	
1990s	· Interferon-alpha (IFN-alpha) in 1994 · Hepatitis C virus (HCV) diagnostic agent in 1995. · Human growth hormone in 1999	· Croserine (anti-tuberculosis)
2000s	· Erythropoietin and Granulocyte colony-stimulating factor (GCSF) in 2001 · Follicle-stimulating hormone (FSH) in 2006	· Zydena (NCE) in 2005 · Sivextro (NCE) in 2014

Source: Interviews (49 and 50 (K-Pharma))

Specifically, Dong-a started to acquire expertise in biotechnology by overseas training in rDNA technology in the early 1980s (in Japan and the US) and by experimental production of diagnostic agents.[177] The development of diagnostic agents aimed at accumulating basic knowledge of biotechnology rather than making profitable products (Interview 49 (K-Pharma)). On this basis, Dong-a started to localise off-patent first generation protein drugs, such as human growth hormone and erythropoietin, in the 1990s.

[177] Overseas training became the main channel of technological learning in the early stages of the company's biotechnology R&D. Over the 1980s and 1990s (until 2002), 12 biotechnology researchers were trained through overseas R&D organisations such as RIKEN (a Japanese leading public institute, the Institute of Physical and Chemical Research) and Otsuka (a pharmaceutical company, the developer of the blockbuster drug Abilify (Aripiprex) for schizophrenia and bipolar disorder).

However, the company missed the right time of entry to build large-scale production facilities for biosimilars and therapeutic antibodies in the early and mid-2000s (Interview 49 (K-Pharma)). This prevented Dong-a from taking the 'first follower' position in the emerging biosimilars business, and it also caused a delay in recouping its long-term R&D investment in biotechnology. In spite of its technological accumulation, LGLS also missed the optimal entry time because it was reluctant to invest in large-scale production facilities for biosimilars in the early and mid-2000s (Interview 35 (DBF)).[178] A large-scale investment in biosimilar production under the commercial and regulatory uncertainty of this emerging market was impossible for small- and medium-sized domestic companies. In the midst of the Korean biotechnology boom, Dong-a belatedly decided to build a new factory for mass production of biological drugs in the form of a joint venture with a Japanese pharmaceutical company, Meiji, in 2011. It will produce a biosimilar of Herceptin starting in 2017.

Overall, although Dong-a is gradually enhancing its imitation-based biological drug business (it has 10 biosimilar or biobetter products in the pipeline), the company seems to need more time to obtain commercial success due to its relatively late start at building production capability compared with competing biosimilar developers.

Interestingly, in the meantime, new entrants such as Celltrion (a capital-intensive DBF) and Samsung are now swiftly trying to take the lead in the emerging global market in biosimilars, while the case firms such as Dong-a and LGLS were more passive in entering full-scale mass production. Remsima by Celltrion, a biosimilar of the rheumatoid arthritis drug Remicade by Johnson & Johnson, became the first monoclonal antibody biosimilar approved by the European Medicines Agency in 2013. Samsung also applied for product approval of two biosimilars of Enbrel and Remicade in the EU in 2015.

2) Other case firms in biotechnology R&D

Other case firms have also shown increasing attention to the biotechnology business beyond small-scale R&D activities. As seen in the case of Dong-a, technological learning generally starts through the accumulation of fundamental genetic engineering techniques by developing diagnostic agents and further localising first- and second-generation protein drugs (GC, Yuhan and LGLS). Other companies have taken similar reverse engineering paths. Hanmi started by attempting mass production of first-generation protein drugs utilising transgenic animals, and moved on to develop DDS for biobetters. Dong-wha, Ilyang and JW have maintained small-scale R&D units for

[178] Interview: the CFO of LegoChem Bioscience, a former manager of LGLS.

biotechnology since the 1990s. On the basis of technological accumulation, the case firms now deal with diverse areas in biotechnology, from biosimilars and cell-culture-based vaccines to new biologics and stem cell research (Table 6.9).

Table 6.9: Biotechnology R&D pipelines of the case firms

Case firm	Pipelines in biologics	Main areas of R&D in biotechnology	Starting year of biotech R&D
Dong-a	13	Biosimilar, biobetters, stem cell	1988
Yuhan	not specified	New biologics, process research	1992
Hanmi	6	Biobetters	1996
CKD	2	Biosimilars, Vaccines	1992
JW	3	Stem cell	1998
Green Cross	1	Vaccines, new biologics, biobetters	1970s
LGLS	12	Vaccines, new biologics, biobetters, biosimilars	1982
Ilyang	2	Vaccines, new biologics	1990
Dong-wha	-	-	1994

Source: Each company's website and IR reports

Overall, diversification into biotechnology R&D can be seen as an effort to overcome the existing organic-chemistry-based technological and market leadership by Big Pharma. The difficulty of developing and marketing NCEs, as the case firms have experienced, leads latecomer countries and firms to discover strong alternative routes to catch up in an emerging biotechnology paradigm.

However, there is a key point that should be recalled concerning this transition. As seen in the previous chapters, biotechnology R&D and its industrialisation involve various innovation actors. That is, successful entry into this new technological paradigm requires collective and interactive learning among diverse innovation actors. However, the collaboration of the pharmaceutical firms with DBFs for biotechnology industrialisation has been limited until very recently, whereas internal learning in biotechnology has increasingly continued.[179]

6.5 Features of Drug R&D in View of Exploratory Learning

This section identifies common features of latecomer firms' new-drug R&D. It focuses in particular on barriers to new-drug R&D and the possibility of overcoming these barriers.

6.5.1 The first round of new-drug R&D

[179] This does not mean that they have never conducted R&D collaboration with DBFs, but indicates a rather passive pattern of collaboration. This is discussed further in Chapter 7.

In the first round of new-drug R&D between 1987 and the mid-2000s, seven NCEs were developed by case firms (Table 6.10). Among these, four NCEs were examined in detail. Failures in three of these cases revealed several obstacles that latecomer firms face in new-drug R&D, particularly in terms of the development of commercially viable drugs. In contrast, the case of Zydena by Dong-a showed how such firms can overcome these obstacles. In this sub-section, these barriers and the possibilities to overcome them are summarised from three perspectives: (a) upstream research, (b) downstream development, and (c) marketing stages.

Table 6.10: Summary of the development of the first new drugs by case firms
(unit: millions of US$)

Brand of NCEs (Firm)	**Indication**	**R&D period (Lead time)**	**R&D investment**			**Cumulative domestic sales** (Sales period)	**Technology Export**
			Internal	NRDPs	Total		
Milican (Dongwha)	Anti-cancer	1995 ~ 2001 (8)	4.3	-	4.3	1.3 (10 years)	-
Q-Roxin (JW)	Antibiotic	1991 ~ 2001 (11)	4.7	0.3 (MOHW)	5 (6%)	15 (10 years)	-
Factive (LGLS)	Antibiotic	1991 ~2002 (11)	50 (GSK :250)	-	300	84 (8 years)	GSK in 1997 -renunciation
Camtobell (CKD)	Anti-cancer	1994 ~ 2003 (11)	13	2 (MOHW)	15 (13%)	12.6 (7 years)	ALZA in 2000 -renunciation
Revanex (Yuhan)	Peptic ulcer	1991 ~ 2005 (15)	37.2	2.8 (MOST)	40 (7%)	42 (6 years)	GSK in 2000 -renunciation
Zydena (Dong-a)	Erectile dysfunction	1997 ~ 2005 (9)	17.8	2.3 (MOHW)	20 (11%)	80 (5 years)	Warner Chilcott in 2009 -in progress
Noltec (Ilyang)	Gastric ulcer	1987 ~ 2008 (22)	26.3	3.7 (MOST /MOHW)	30 (12%)	2.8 (2 years)	TAP in 2005 -renunciation

Source: Own elaboration based on data from several sources

a) During upstream research, all firms were faced with a lack of capability needed to identify targets and develop lead compounds. They had few experienced researchers and relatively few funds to invest in R&D. Although they had accumulated strong imitative capability through localising APIs, drug discovery needs advanced scientific research beyond the process technologies.

Thus, under this limited research capability, modification of existing lead compounds (that is, the me-better strategy) was adopted as a way to lift the barrier of drug discovery.

The latecomer firms could thus skip upstream research on target and lead identification and reduce technological risk. They could finally derive improved drug candidates based on existing lead compounds. However, this strategy generally failed to generate satisfactory commercial outcomes, and the firms were unable to decrease the development time gap against revival products due to their overall lack of research capability. In addition, the prolonged development lead time made it difficult to penetrate the market.

In contrast, the case of Zydena by Dong-a shows how this upstream research barrier could be overcome, even as Dong-a followed the same me-better strategy. Dong-a actively utilised the prior knowledge base it had accumulated from previous failed projects.

b) In terms of downstream development, the case firms were unable to complete multinational clinical trials. Big Pharma companies that acquired case firms' drug candidates for global development saw low market potential, while the clinical development of licensed-out drugs was directly affected by changes in the global pharmaceutical industry's competition structure, such as mergers and acquisitions. Renunciations by Big Pharma resulted in the failure of global development of locally derived NCEs. It also caused a delay in the development lead time and apathy toward the NCEs after their local NDA in the domestic market.

In contrast, Dong-a recognised the importance of lead time for drug development as a critical factor in the me-better strategy; a short lead time would allow a me-better drug to be included in the first tier of follow-up NCEs to the first-in-class NCEs (such as Levitra and Cialis, in the case of Viagra). They were less attached to global development, prioritising the domestic market. In so doing, they narrowed the time gap to market launch between their drug and the first-in-class drug. They were also able to avoid absolute subordination to the development leadership of Big Pharma.

c) From the perspective of marketing, the three NCEs failed to generate expected market profits. This was due to the cumulative results of the delay in drug identification, the focus on a more competitive market, reliance on Big Pharma and a failure to reflect changing market needs in the R&D process.

On the other hand, Dong-a developed Zydena for a niche market segment with a weak degree of market competition. This allowed the company to penetrate the domestic market and create successful profit in a fairly smooth manner; Domestic success then

bolstered their technological credibility, which aided further global development. Zydena is being launched in Brazil in 2015 and in the process of product approval in the US.

Overall, an analysis of the first round of new-drug R&D shows that technological barriers can be overcome to some extent over the course of a long R&D process. However, it also reveals the technological success finally gained cannot be proportionately translated to market performance if the R&D process does not reflect market needs and the global competitive environment.

6.5.2 The second round of new-drug R&D

The second round of new-drug R&D was started in response to the commercial failure of the first round of new drugs, and the changing institutional environment. This round saw diversification of drug R&D, moving away from NCE development for the major markets. Four alternative R&D pathways were identified: incremental innovation through IMDs, niche NCEs related to QOL, traditional medicine-based phytomedicines and biological drugs in both imitative and innovative areas (Tables 6.11 and 6.12). This diversification can also be seen by looking at the distribution of R&D personnel in the KoPI (Table 6.13).

Table 6.11: Diversification of R&D pipelines

Case firms	Chemistry-based R&D					Biotechnology R&D	
	Own DDS	IMD	NCE in QOL	Anti-cancer/ Antibiotics	Phytomedicine	Biologic	Vaccine
Dong-A	○	2	9	1	2	8	○
Yuhan	○	6	10	2	3	○	-
Hanmi	○	11	-	5	-	6	-
CKD	○	6	3	2	○	1	1
JW	○	10	3	2	-	○	-
Green Cross	-	-	1	-	1	9	3
LGLS	○	-	9	1	-	7	5
Ilyang	○	2		2	-	○	○
Dong-wha	○	-	4	2	2	○	-

Source: Own elaboration based on data acquired from each firm's annual reports

The incremental innovation path of IMDs could maximise prior imitative capability (i.e., process technologies) without full-scale exploratory research. This path was rapidly established to deal with institutional changes, such as the introduction of SPD. Similarly, the recent boom of phytomedicine R&D is seen as a way to minimise technological risk in drug discovery through 'scientifying' the herbal plants that are already used locally. At the same time, the focus on NCE development has shifted to the less-competitive QOL-

related diseases, which represent a niche market opportunity. Lastly, companies are paying more attention to biological drugs in an effort to overcome the technological limitations in synthetic drug R&D and the industrial dominance by Big Pharma.

This diversification reveals an experimental diversity in the latecomers' technological catch-up in the science-based and Big-Pharma-led pharmaceutical industry. As seen, the first new drugs often failed commercially after 10 to 20 years of R&D. The analysis in this chapter has shown that a single focus on technological performance hardly secured the creation of significant profit sources or a successful transition. Companies therefore diversified in an effort to find more realistic innovation paths to overcome the transitional barriers. This will be discussed in depth in Chapter 8.

Table 6.12: Patent trends of all case companies, by R&D field

	R&D fields	1960s	1970s	by 1987	1988-1999	2000-2010
Chemistry	NCEs (Innovative & derivatives)	-	-	1	129	147
	Phytomedicine	-	-	-	10	16
	IMDs (DDS, composition, structure)	-	-	-	82	174
	Process development	4	20	80	137	132
Biotechnology	Product (& materials)	-	-	1	135	112
	Method	-	-	5	140	92
Total number of patents		4	20	86 (1%)*	633 (56%)*	673 (66%)*

* The ratio of non-process development related patents (i.e., closer to product development)

Table 6.13: Distribution of R&D personnel in the KoPI, by product field

	R&D fields	2009	2010	2011
Chemistry	NCEs	1,186	1,214	1,290
	Phytomedicine	431	477	605
	IMDs	1,170	1,190	1,251
	Generics	1,404	1,528	1,684
	APIs (Bulk drugs)	473	425	445
Biotechnology	New biologics	553	591	594
	Biobetters	224	243	284
	Biosimilars	320	328	353
Total number of researcher		5,760	5,996	6,496

Source: KHIDI (2011)

6.6 Summary

This chapter discussed the latecomer firms' new-drug R&D processes, which were characterised by the commercial failure of their first in-house-developed NCEs, and subsequent diversification into new-drug R&D paths.

An analysis of the first round of new-drug R&D, which failed to produce a market profit from firms' first NCEs, identified three major barriers to technological learning. The first barrier was the absolute lack of upstream research capability. Because of this, latecomers largely adopted a me-better strategy, trying to produce their own versions of existing NCEs in popular market segments to overcome their limited scientific research capability. Second, Korean firms' lack of development capability led them to simply transfer their technology to Big Pharma, which resulted in the subordination of development leadership to potential competitors. Third, their new-drug R&D activities failed to reflect downstream market factors.

The second round of new-drug R&D involved the deployment of four diversified paths, which was more realistic in terms of creating market profitability. Firms hoped to overcome the barriers encountered in the first round of new-drug R&D by focusing on niche markets and allocating their projects to various drug categories: Short-term incremental innovation through developing IMCs, QOL-oriented NCE development as a long-term innovation source, phytomedicine development as a mid- and long-term profit source and biotechnology R&D to reap the benefit of the changing technological paradigm.

Overall, this chapter showed the latecomer firms' awkward practice of an exploratory mode of technological learning in their new-drug R&D process. In terms of R&D strategy, it also showed that technological learning never allows proportionate market catch-up if it does not match the changed catch-up environment in the transitional phase.

Chapter 7: Organisational change in New-drug R&D

7.1 Introduction

This last empirical chapter presents the alignment process of the organisational structure with the new drug R&D activities.[180] It points out that the delayed change of the organisational structure compared to the changing nature of technological learning toward exploration partly led to the problematic new-drug R&D process. This chapter consists of a single main section (Section 7.2).

7.2 Organisational Structure for New-drug R&D

This section addresses the changes in organisational structure to deal with new drug development. Specifically, it focuses on whether or not organisational structure has been rearranged with the same pace and proper form, as the case firms expand new drug R&D activities over the first and second rounds of new-drug R&D. In conclusion, organisational structure is revealed to have been altered in a late tempo compared to the changing mode of technological learning. The main focus is Dong-a's case of organisational change as this is the most successful (Sub-section 7.2.1). This is followed by examples of other firms (Sub-section 7.2.2). It adds two exceptional cases that operate independent R&D organisation for conducting long-term drug research as small latecomers (Sub-section 7.2.3).

7.2.1 Change in the R&D organisation of Dong-a

In the 1980s: During the reinforcement of the product patent system in the 1980s, the simple development organisation of final products was first expanded into the fundamental steps of drug R&D, such as the synthetic research and toxicity test (from Figure 7.1a to Figure 7.1b). The expansion of R&D organisation mainly focused on the analysis and localisation of existing drugs and partly on synthetic chemistry research related to new drugs. Biotechnology research units were also set up during this period.

Between 1987 and 1998: The most substantial start of new-drug R&D began after the enlargement of the R&D centre in 1987. Figure 7.1c shows that new-drug R&D had been conducted under the function-based organisational structure in that period (between 1987 and 1998). Organic synthesis, pharmacology and safety tests were conducted by

[180] This organisational perspective has scarcely been treated as the main perspective in understanding latecomers' catch-up in the literature, as the focus on technological learning activities has provided sufficient in-depth understanding of the successful catch-up by Asian NIEs.

individual teams, devoted to these specific functions, respectively. This was partly a result of the incremental entry strategy for new-drug R&D under the main focus on imitative development of generic drugs based on the function-based structure.

Between 1998 and 2002: At the beginning of 1998, Dong-a rearranged the R&D organisation by introducing a mixed organisational form of function (e.g., safety team) and project (organic drug teams) (Dong-a 2002) (Figure 7.1d). Through organisational change, they highlighted the importance of "reality based R&D activity and its advancement", rather than aiming at setting up an organisation for long-term R&D (Interview 48 (K-Pharma)).[181] In fact, it was to speed up the development of commercially viable drugs by making the competition structure between organic drugs teams (Interview 48 (K-Pharma)). The continuous failure of upstream drug research, and the economic crisis in late 1997, underlay the trial of organisational rearrangement. It exposed the difficulty of holding up innovative R&D in the long-term as a small size latecomer firm.

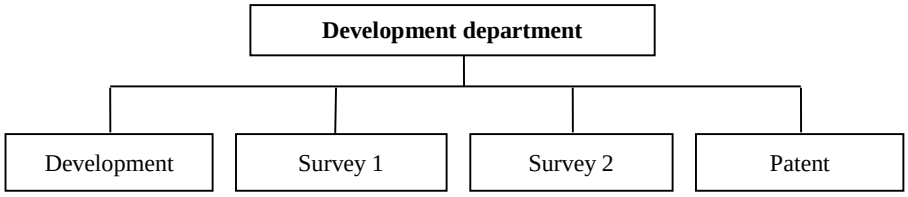
Between 2002 and 2007: The R&D centre was later reorganised by the division of the R&D field in 2002 (Figure7.1e). This period is viewed as the beginning of the full involvement of new-drug R&D: a drug research division (based on organic chemistry), biopharmaceutical division (based on biotechnology), and product development division (which included most imitative development and in-licensed drugs). In the drug research and biopharmaceutical divisions, each team was comprised of an R&D project base rather than a function base. The organisational design delineated the main functions of drug research into a team, and was intended to promote interactions between functional areas, such as synthesis and pharmacology (Interview 49 (K-Pharma)). The CTO pointed out the continuous change in organisational structure was mainly due to the ongoing underperformance of their upstream research.

Between 2007 and 2012: The organisational structure shows a more sophisticated and enlarged form of the previous project-based R&D organisation (Figure7.1f). The differences from the previous form are the transfer of a preclinical evaluation team from the product development division to the drug research centre, and the establishment of an independent phytomedicine team.[182] In particular, the former change was intended to agglutinate the upstream and middle-stage research.[183] The latter, as seen, reflects the innovation strategy of Dong-a, focusing on a niche market based on the success of its

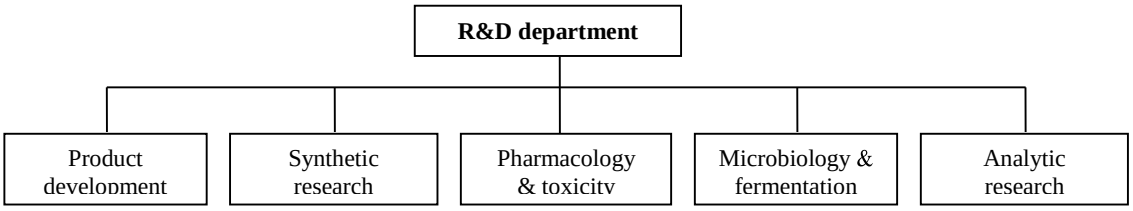
[181] For example, the development of economically high added APIs, such as cycloserine and ondansetron, which indicated the achievement of more successful imitative R&D.
[182] The product development research centre is mainly devoted to developing IMDs and DDSs.
[183] The phytomedicine research unit moved to the product development centre in 2012.

first phytomedicine, Stillen. Overall, the present R&D organisation reveals an incremental transformation of the R&D organisation that seems more suitable for conducting more interactive learning between each function of new drug R&D.

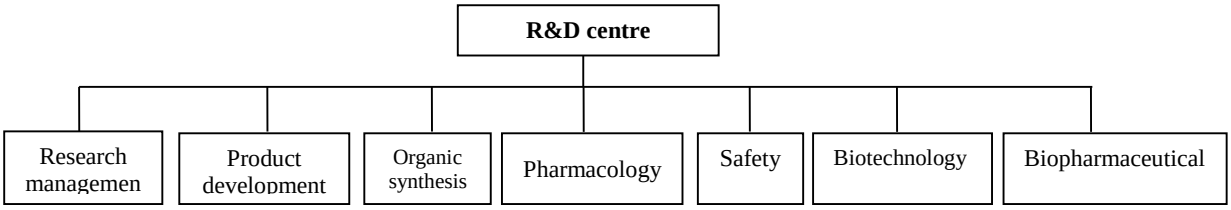
a. Until 1984



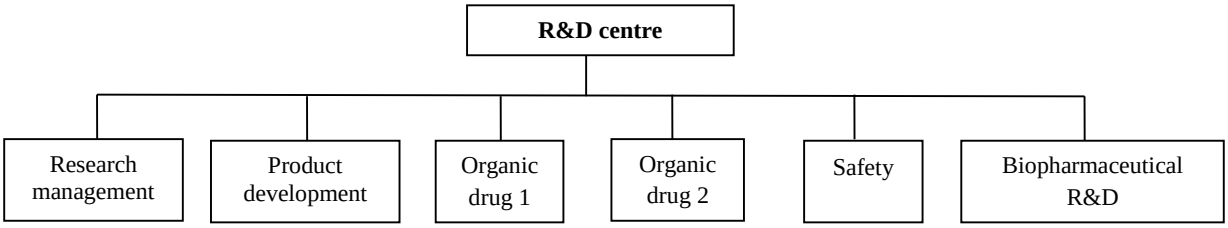
b. Between 1985 and 1987



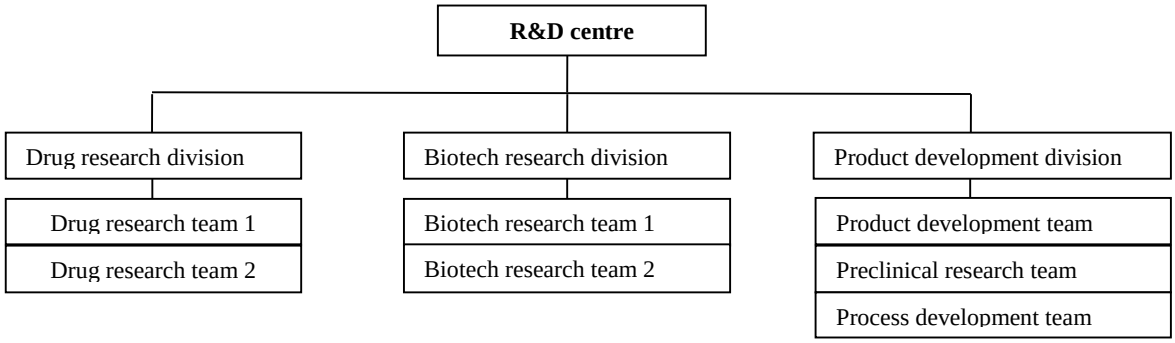
c. Between 1987 and 1998



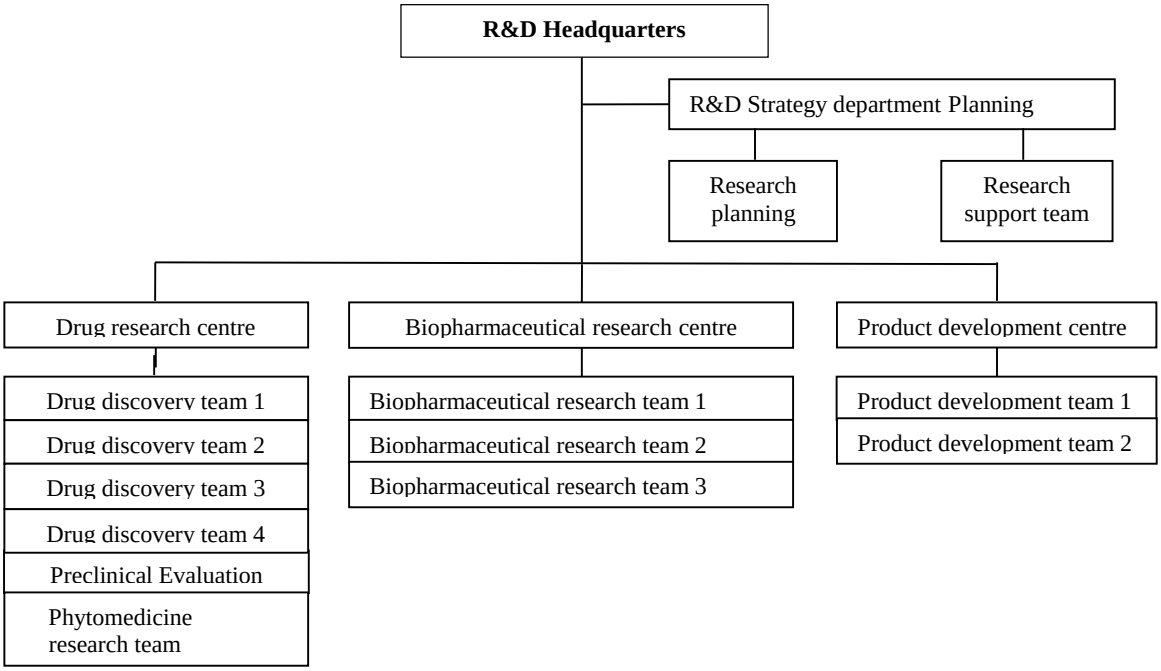
d. Between 1998 and 2002



e. Between 2002 and 2007



f. 2007 and 2013



g. In 2013

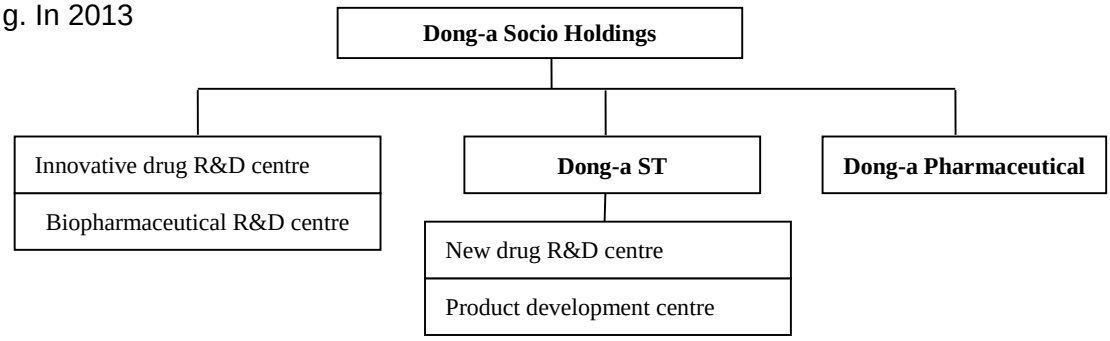


Figure 7.1: The change in R&D organisation of Dong-a

Sources: Interviews and internal reports, company website, and Dong-a 70 years (2002)

Late establishment of R&D organisation for systemic new-drug R&D

In the present form of the R&D organisation (Figure 7.1f and g), three managerial decisions are worth noting in view of exploratory learning.

(i) First, the newly launched R&D committee, formed in 2009, consisted of seven senior managers from the headquarters (or departments) of research, development (for clinical development), production, management planning, marketing, and international business. Monthly meetings checked progress and determined the possibility of launching new-drug projects and whether on-going projects should be continued or dropped.

In 2011, the decision was made through the R&D committee to drop a pipeline product that had completed its clinical phase I, despite an R&D investment of about US$6 million

(i.e., about 10% of the total R&D expenditure in 2011). The abandonment of this project was attributed to the lack of commercial viability in the global market.

It is particularly important to note that the company had begun to reflect market trends in their R&D processes in a systemic manner. While dropping this type of project is not uncommon in Big Pharma, it was the first time for Dong-a. Prior to this, most projects were dropped in the R&D process due only to technological reasons (e.g., derivation, toxicity, or efficacy), as shown earlier. More specifically, factors on the downstream side, such as demand changes in the targeted market, seldom influenced the decisions at each R&D stage. The first round of new-drug R&D revealed this perspective.

(ii) Second, the small R&D centres were based on their R&D fields (NCEs including phytomedicine, IMDs and DDSs) with the underlying tone of competitive resource allocation. Allocation of R&D investment to the three R&D centres became based on their performance. That is, the firm introduced a kind of competition system between small research groups, with the aim of speeding up the R&D process. This type of small research group-based organisational management was operated by GSK in various pipeline products.[184] However, it is unclear that the competition structure would encourage the long-term exploratory R&D.

(iii) Interestingly, in 2013 Dong-a reallocated the three R&D centres into the two companies. The R&D centres of biotechnology and innovative new drugs were placed under the Dong-a Socio Holdings, the holding company of all Dong-a subsidiaries. R&D centres of (me-too/better) new drug R&D and product development were allocated in Dong-a ST (Science and Technology), which focused on the ethical drug business. The reorganisation of R&D centres indicates the rearrangement of drug R&D depending on the degree of exploration and possibility of commercialisation. The former R&D fields, innovative new drug R&D (first-in-class) and biotechnology R&D, requires higher technological and business risk than the latter R&D. Thus, placing the former R&D in the holding company seemed to secure its stability of long term research investment. The case of LGLS showed the direct influence of the commercial failure of Factive on later R&D projects under the same organisational boundary. The following examples of GC and JW support the effectiveness of the division of R&D organisations depending on their nature of technological learning.

On the whole, the change in organisational structure at Dong-a has shown that an exploratory mode of technological learning has been run in parallel with managerial

[184] Comment by the CEO of GSK, Andrew Witty (ChosunIlbo 13/10/2010).

efforts to design an "appropriate" organisational structure. The most noticeable change in R&D organisation was not just the physical enlargement of the R&D centre but also the change in organisational structure from function-based to project-based, adding the characteristics of a matrix organisation.

However, determining whether or not this organisational change has been sufficiently synchronised with their exploratory learning is difficult. Rather, their organisational change can be said to be laggard, as a post-response to the continuous failure of new-drug development, not as a pre-emptively designed R&D organisation, at least until the middle of 2000s. The practical change in organisational structure, that could comprehend the main functions of new-drug research within a team for more interactive and prompt responses, was not formed until 2002. Furthermore, full-scale organisational change has been conducted within the last few years, since 2007.

7.2.2 Lag in restructuring R&D organisation

Firms in other case studies reveal the lag in synchronising the organisational structure with their rapidly expanding exploratory learning more clearly. Many case firms have recently started to change their R&D organisation after their continuous failures in innovative R&D, which had been operated under the function-based R&D organisation. Herein, the internal estimation of their organisational structure in new-drug development (e.g., Yuhan, CKD) is presented briefly.

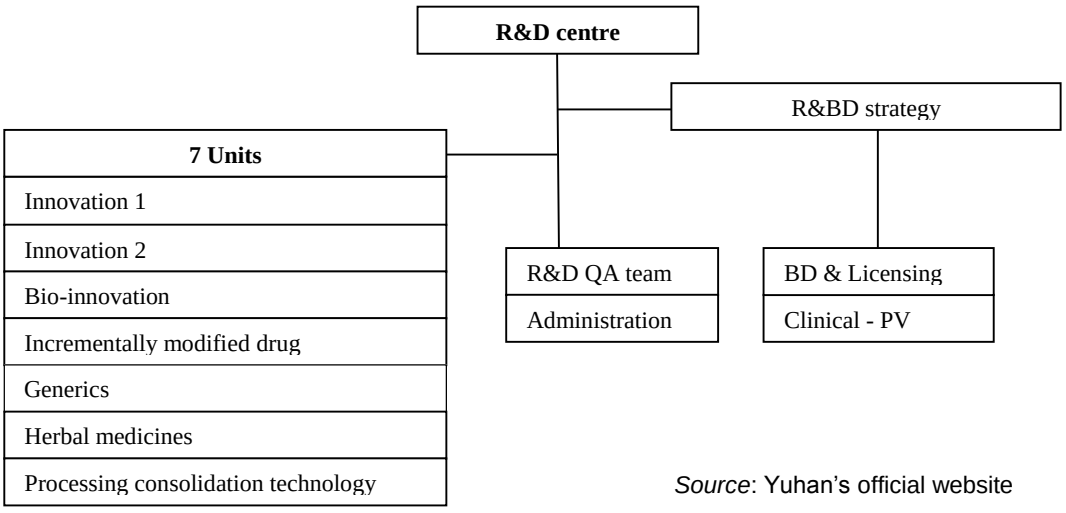


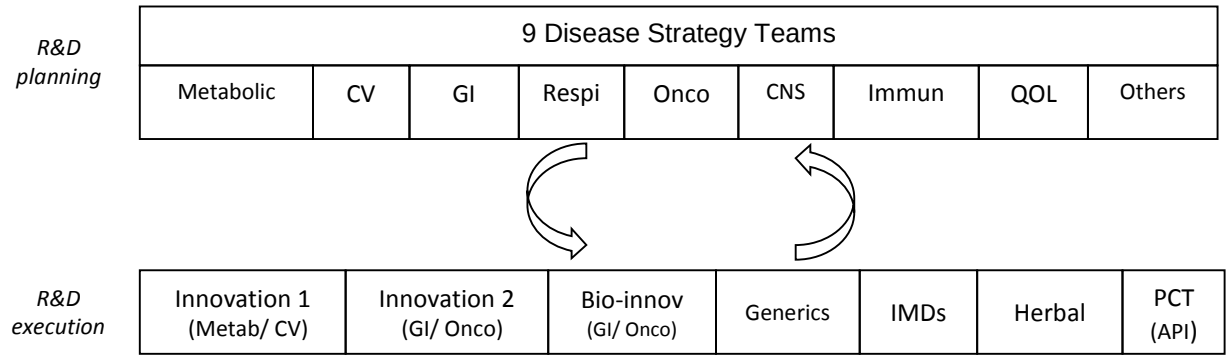
Figure 7.2: The organisational structure of the R&D centre of Yuhan (after 2009)

First, in 2010 Yuhan completely reformed their R&D centre into a project-based organisation (Figure 7.2). This reconstitution was linked to continuous failures in their pipeline products after the development of their first drug, Revanex, in 2004. They were

faced with the absence of any prominent pipeline products in the second or last phase of clinical trials (Interview 46 (K-Pharma)). Prior to the change, their innovative R&D had mainly been operated as a functional-based organisation. To solve the static R&D process in a function-based R&D organisation, they introduced a unit-based matrix organisation, rather than one that used departments or teams.[185]

The firm has also established an interdivisional strategic team, called the disease strategy team (DST), which consists of leading researchers, developers, marketing specialists, and clinicians for planning and checking on their R&D and commercialisation strategy across nine areas of disease. The DST was initially set up to probe unmet medical needs, and to monitor the potential for commercialisation of their pipeline products in the nine disease areas on which the company has focused. On the whole, through both the execution units of the real R&D activities and the monitoring of DSTs, they intended to develop a dynamic reflection system of the clinical and market information on the R&D process (Figure 7.3).[186]

Therefore, the DST meeting can be regarded as a similar organisational form to the R&D committee newly established by Dong-a. It should also be noted that the recent reformation was led by a newly-scouted executive director (for R&D strategy) from Big Pharma of Bristol-Myers Squibb (Dr Su-yeon, Nam, who worked as a global medical director in 2009) (Interview 46 (K-Pharma)).



Source: Material acquired in the interview

Figure 7.3: The operation of the R&D organisation of Yuhan (after 2009)

[185] Comment of the CTO of Yuhan, adopted from DailyPharm, 2/5/2011. The concept of unit seems to stress the dynamics and coherence of drug research-related functions within each drug development project, based on the interviews.

[186] In Figure 3, CV – cardiovascular, GI – Gastrointestinal, Respi – respiratory, Onco – oncology, CNS – central nervous system, and Immun – immunology.

In the case of CKD, no data for substantial organisational structure were acquired. However, interviews with their CTO confirmed that their R&D organisation had also been entirely restructured in the rapid enhancement of innovative R&D. In 2011, three small R&D centres were formed: a new drug research centre, a biotechnology research centre, and a formulation research centre. This is a similar organisational structure to that of Dong-a.

In each research centre, the interaction between R&D functions is stressed for efficient new-drug R&D. The scouted head of the new-drug research centre, Dr Sung-gon Kim, former researcher at Merck, emphasised the importance of interactive research activities between functions:

> In the past, our (Korean firms) new-drug R&D was considerably retarded because each research stage did not simultaneously or immediately provide feedback for each other under the function-based team structure. Between the functional teams, a time lag was caused when the research outcomes were transferred to the next steps and further, feedback from other functional teams also lagged. Now we are really trying to build better organisational structures that can encourage the interactive research activities between medicinal chemistry, pharmacology, toxicity, formulation, and so on (Interview 51 (K-Pharma)).

In short, the function-based compartmented R&D activities caused a lowering of interaction between each R&D step. This has been one of the critical factors degrading the commercial potentiality of new drug R&D activities by latecomer firms. Interestingly, this point was particularly emphasised by the interviewees who had experienced the R&D activities in Big Pharma (Interviews 34, 38 and 51). The CTO of Yuhan points out the degradation of interactive R&D and translational research between upstream and downstream R&D:

> At present, researchers tend to concentrate only on their main tasks. Chemists only conduct chemical research in the laboratory. Animal experimenters only implement toxicity tests. In this routine, research outcomes are not shared and integrated until the completion of clinical trials. Thus, if the company doesn't acquire the expected R&D outcomes in the clinical development, they have to go back to the first step and do it again. R&D progress should be monitored and discussed in every step between different functional researchers and then the

company can derive more prompt alternatives. Time and cost efficiency can be achieved by conducting such translational research.[187]

The case of LGLS provides an understanding of the practical operational mechanism of the changing R&D organisation: the matrix form of R&D organisations in the mix of project and function that underlie the recent rearrangement of the R&D organisations in most case firms, although it is a rough sketch based on interviews (Figure 7.4) (Interview 37 (*Chaebol*)).

As seen, in 2006 they turned their R&D focus from competitive antibiotics to QOL drugs due to the influence of the marketing failure of their first new drug, Factive. In line with this, their R&D organisation was converted to a matrix of project-based (i.e., disease area-based) R&D research groups. The formal R&D organisation is comprised of the R&D functions (i.e., technological category-based research groups, generic development, pharmacology evaluation, and clinical development). On this basis, as the pool of R&D personnel, their real drug development projects are conducted by forming the transitory project groups that depend on pipelines and R&D progress.

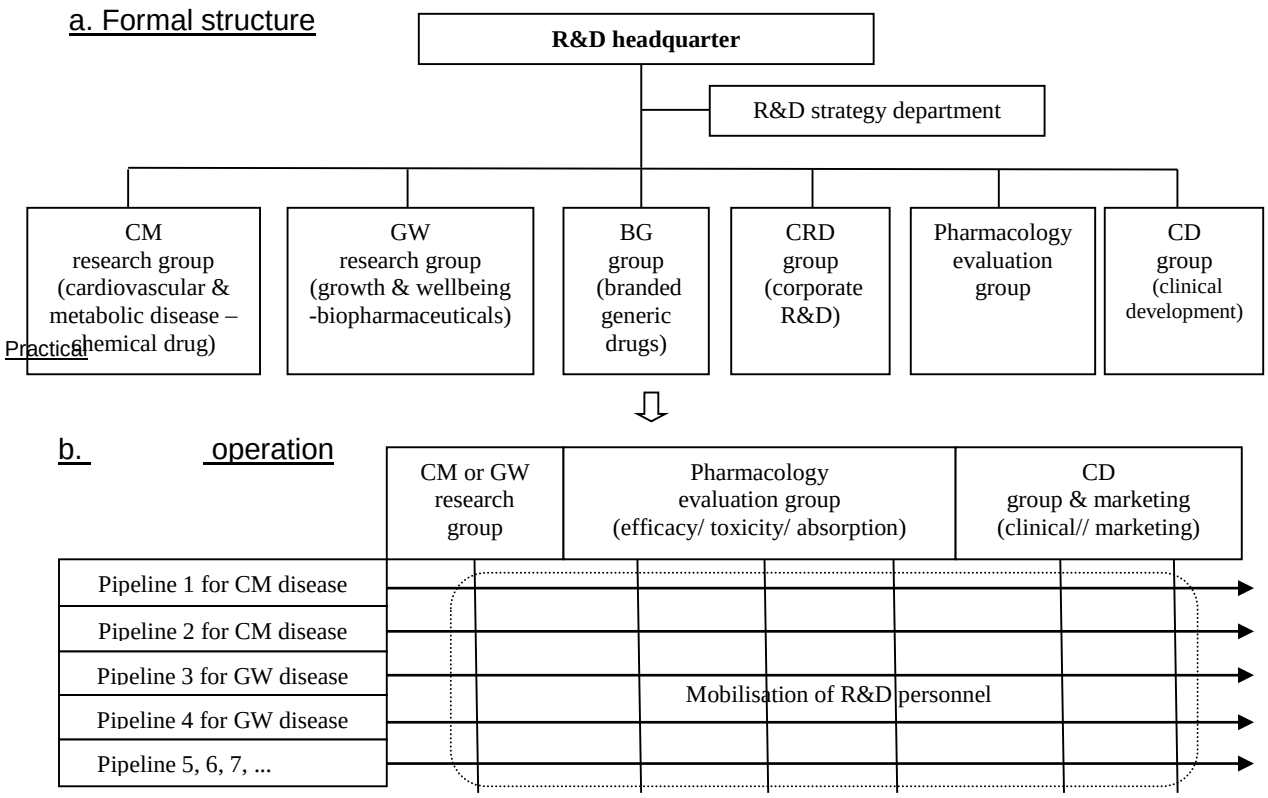


Figure 7.4: The organisational structure of the R&D centre of LGLS

[187] Speaking in the Seoul New Drug Development Conference in 2010.

Overall, although detailed organisational structures differ across the case study firms, they also show broad commonalities (Table 7.1). First, their present organisations for new-drug R&D were purposefully designed to facilitate more integrative/interactive R&D activities between upstream and downstream R&D functions in each drug development project. Second, the reformed R&D organisations show the dual R&D strategy that comprehends both new-drug R&D and the development of generic drugs, but with intentional separation of these two tasks. In most of these firms, generic drug development is deployed in the product development division. Lastly, it should be remembered that these organisational efforts are the evolutionary result of the continuous failure in new-drug R&D under the function-based R&D organisation, and thereby the weak interaction between R&D functions.

Table 7.1: Summary of the restructuring of internal R&D organisations

Name of firm	Number of R&D centres (in 2010)	Organisational structure	Year of the organisational change	Year of starting innovative R&D
Dong-a	3	Project and Matrix	2007	1987
Yuhan	1	Project and Matrix	2009	1987
Hanmi	3	Project	2010	2000s
CKD	3	Project and Matrix	2010	1987
JW	3	Project	2007	1987
Green Cross	2	Not identified	-	1970s
LGLS	6	Project and Matrix	2006	1987
Ilyang	1	Function	-	1987
Dong-wha	1	Function	-	1987

Source: Data from various documents

7.2.3 The arm's length R&D organisation

Lastly, the other firms under study, Green Cross (GC) and JW, have shown notable differences in their way of maintaining R&D organisations for upstream research, which has been one of the fundamental obstacles to new-drug development. While other firms have managed upstream research organisation under their direct command as central R&D centres, GC and JW have tried to deepen the upstream research through a dual approach by maintaining both the central R&D centres and independent organisations devoted to upstream research. These two examples support the effectiveness of autonomous R&D organisation in sustaining exploratory learning, as the literature argues.

GC established the Mogam Biotechnology Research Institute (MBRI), Korea's first privately funded non-profit research institute, in 1984, and JW set up a drug discovery

oriented JV, C&C, with a Japanese company (Chugai Pharmaceuticals) in 1992.[188] Until now, they have concentrated on upstream and mid- and long-term research, escaping their mother companies' direct control and market performance. Interestingly, the present pipeline products of these two companies are mostly involved in the first, or best, class of drugs that aim to penetrate the global market, and many of their pipelines have been first established based on drug identification by external R&D organisations.[189]

The establishment of MBRI as an independent research institute was the decision of the owner after the commercial success of the in-house developed hepatitis B vaccine (Hepavox - the third hepatitis B vaccine developed worldwide). MBRI has operated on royalties from their research performance that have been mainly transferred to their parent company, GC. The institute also holds about 10% of the shares of the holding company of GC. Through establishing an independent R&D entity, on the one hand they have come to provide researchers with a more autonomous research environment. On the other hand, GC has been able to secure their explorative research activities, freed from its own market performance. That is, GC has tended to save their profits from *Hepavox* to secure the continuation of upstream research that has been interrupted by the external economic situation and GC's annual market performance:

> The former chairman, my late father, aimed at setting up a reservoir of technological sources both for society and for us (GC). In reality, MBRI has played as a dam for GC in the last three decades. When we (GC) have made a surplus in market profit, we've stocked this in Mogam and thus they have been able to continue and expand their research. On the contrary, Mogam has played as a stronghold of R&D activities when we (GC) have been stuck in difficulties in market performance or other factors (Interview 40 (K-Pharma)).

Overall, GC's present R&D organisation is comprised of the directly-commanded R&D centre of GC and the indirectly-controlled MBRI, through an arm's length transaction. The latter concentrates on mid- and long-term upstream research, and the former focuses on short- and mid-term downstream R&D. In short, almost half of GC's publications were conducted by MBRI. As a result, their long-term research has been secured through MBRI.

Although the case of JW is not exactly the same as GC, it also shows the possibility of the successful management of explorative research. Through the successful foundation

[188] The institute has been registered as a collaborating research centre of WTO in vaccines and diagnostic agents since 1989.
[189] Example: the first in class NCE candidates – GCC1290K by GC and CWP231A by JW.

of C&C with Chugai, JW was able to accumulate upstream research-related technologies and knowledge, such as screening technologies, CADD (Computer Aided Drug Design), ADME and efficacy test, IPR management, and project and pipeline management, including clinical development. C&C has provided eight drug candidates for JW and Chugai in the last 20 years.[190]

7.3 Summary

This chapter has addressed the restructuring process of organisational structure to deal with increasing new-drug R&D activities. Internal R&D organisations and, at times, arm's length R&D units were analysed.

First, the analysis showed that organisational structure of R&D centres is a somewhat later response to the changing nature of technological learning, from exploitation to exploration. The function-based organisational structure disturbed the interactive learning between R&D teams and did not adequately reflect market changes. Most case firms have belatedly transformed their function-based R&D centres to project- (product) based R&D organisations, adding matrix forms. This was a response to the continuous failures in linking their exploratory learning with their commercial outcomes.

Second, the analysis presented the effectiveness of arm's length R&D organisation for continuing long-term upstream research. GC and JW have operated entities independent of the explorative upstream research organisation, in parallel with their central R&D centres. In doing so, they have, to some extent, been able to secure autonomous and mid- and long-term research environments.

The following chapter answers the research question of the factors that influenced the enhancement of an exploratory mode of technological learning, taking into account both the macro-level policy perspective (Chapter 5) and firms' organisational perspective (Chapters 6 and 7).

[190] Furthermore, in 2000, JW launched a new R&D centre (Theriac Pharmaceutical) in Seattle, USA, that concentrates on more upstream oriented research (target identification and validation, and drug discovery), based on the newly emerging proteomics and chemical genomics. At the same time, they are in charge of the clinical development of their first-in-class pipeline product in the US (CWP231A, the first inhibitor of Wnt signalling pathway, for treating acute myeloid leukaemia, now in clinical trial 1).

Chapter 8: Analysis and Discussion

8.1 Introduction

This chapter discusses the institutional and organisational factors that have influenced the enhancement of the exploratory technological learning that drives industrial transition from imitation to innovation. The conceptual framework used in the thesis was built on a transformative view of institutional and organisational mechanisms that can promote exploratory learning (Chapter 3). The institutional and organisational elements discussed were determined based on the literature review. The empirical case studies then examined the process of institutional and organisational transformation and its positive and negative effects on exploratory learning (Chapters 4, 5, 6 and 7). This chapter discusses the empirical findings through the lens of the literature review and the conceptual framework. Prior to this discussion, the thesis's research questions are recalled:

RQ 1: How have S&T policy rearrangements affected innovation actors' enhancement of the exploratory mode of technological learning?

RQ 1.1) How have the reformed S&T policies influenced exploration practices within organisations?

RQ 1.2) How have the reformed S&T policies influenced interactive learning between public and private innovation actors?

RQ 2: How have latecomer firms strengthened the exploratory mode of technological learning for new-drug R&D?

RQ 2.1) How has the exploratory mode of technological learning been reinforced in new-drug R&D practices?

RQ 2.2) How have organisational mechanisms been reconfigured to deal with exploration-driven new-drug R&D activities?

The pattern of institutional factors that influences exploratory learning is first discussed in relation to RQ 1 (Section 8.2). The following section (8.3) illuminates the firm-level organisational factors necessary to proceed with exploratory learning, seeking to answer RQ 2 (Section 8.3). This is followed by a summary in Section 8.4.

8.2 Institutional Factors Influencing Exploratory Learning

This section discusses the research findings in relation to the influence of S&T policies on exploratory learning (Research Question 1). To do this, the prior literature is briefly compared to the findings of the empirical analysis (Sub-section 8.2.1). The effects of the S&T policy revisions on exploratory learning are then discussed in detail (Sub-sections 8.2.2 to 8.2.5), followed by a summary of the overall findings (Sub-section 8.2.6).

8.2.1 Literature and empirical findings

- Institutional complexity surrounding exploratory learning in literature

Exploration is generally seen as distant search and learning in order to create novel products and processes. This goes beyond latecomers' traditional proximate search and learning associated with the refinement of existing products and process, that is, exploitive learning (Chapter 2, Sub-section 2.2.3). The literature on exploitation and exploration, on the one hand, emphasises the complementarity of the two modes of learning; they are the source of both today's profit creation and tomorrow's survival. Once the outcome of exploration is translated into a novel product or process, the learning mode then changes to exploitation to improve quality and economic efficiency. On the other hand, the literature also points out the mutual exclusivity of the two modes of learning, particularly given the limited resources available to most organisations. They have different learning goals and processing mechanisms, and require different institutional and managerial conditions.

The literature review on successful catch-up in Asian NIEs showed how relevant policies can be effectively deployed to support the incremental increase of exploratory learning, starting from an initially 'extreme' focus on exploitive learning (Chapter 2, Sub-section 2.3.2). This typically involves the vertical composition of S&T and industrial policies to support technological learning and market penetration. Under the classic catch-up framework, innovation actors, such as *Chaebol* in Korea and SMEs in Taiwan, were intensively fostered, allowing them to gradually strengthen technological exploration and rapidly create market profit. Modular architecture-based industries, such as the electronics and ICT industries, are classic cases of this type of incremental transition.

Meanwhile, the literature on science-based innovation highlighted the complex institutional setting surrounding technological learning in the pharmaceutical industry. This institutional complexity stems from three features of sectoral knowledge dynamics. First, pharmaceutical innovation is based on intense scientific research, meaning that firms must typically draw on a wide range of public research institutes and universities.

Public actors have different incentives and behavioural rules from industrial actors, leading to institutional complications in a pharmaceutical SIS. Second, the proliferation of new biotechnology-based drug discovery paradigms also increases the complexity of industrial organisation, previously led by synthetic chemistry-based pharmaceutical companies, because of the increasing influence and importance of biotechnology-based start-ups and public institutes. Finally, the nature of the integral product architecture of drugs necessitates horizontal and cohesive networks between these innovation actors.

Consequently, the literature review implied that one might expect significant challenges in dealing with the institutional complexity of the pharmaceutical industry's transitional phase. Common barriers present in the transitional phase, such as the wide distance between the imitation and innovation stages, are intensified in the pharmaceutical industry due to sector-specific knowledge dynamics.

In this regard, the literature review raised the importance of changing institutional settings to promote technological exploration. In particular, the review indicated that the key characteristics of exploratory learning should be accommodated in the latecomers' institutional rearrangement for a science-based transition.

- Institutional influence in empirical analysis

The empirical analysis showed both the applicability and the limitations of the literature. A few historical experiences of the KoPI support the analysis in the literature. First, the empirical analysis showed that a positive institutional role can be played in the imitation stage, particularly in relation to incentive policy, to strengthen exploitive learning. The mastery of production technologies for existing drugs was sped up by the import substitution industrialisation (ISI) policy and a loose IPR regime. These policies support the argument of that a favourable institutional environment must be nourished for rapid catch-up in Korea. Second, the focus on supporting emerging biotechnology is consistent with the argument about latecomers' opportunities to take advantage of new technological paradigms by quickly moving to them, rather than sticking with the dominant technological paradigm. Third, the overall effort to reform S&T policies supports the general suggestions about the institutional conditions for science-based innovation found in the existing literature.[191]

- Limitations in interpreting the institutional influence on exploratory learning

[191] For example, the KoPI witnessed the reinforcement of the IPR regime, that of R&D investment, to science, fostering DBFs and a risk-capital funding system like the venture capital system found in the USA.

However, the empirical findings of the thesis are only partially explained by the prior literature on catch-up and science-based innovation in terms of understanding the micro-level influence of institutional factors on exploratory learning.[192]

First, the influence of the reformed S&T policies on the exploration practices was rarely subjected to in-depth empirical analysis in the prior literature, particularly in relation to science-based industries with integral architecture products. The literature mostly focused on addressing the institutional mechanisms that led to the successful catch-up that mainly took place in modular architecture-based industries (e.g., Choung et al. 2006, Choung and Hwang 2007, Forge and Bohlin 2008). Second, the increasing intervention of non-industrial institutional spheres in industrial catch-up, such as the public science and public health systems, was often overlooked in the existing studies.[193] Third, the complication of relevant policies, often due to the involvement of several governmental ministries, and its impact on attempting a 'transformative/discontinuous' pattern of technological learning in the latecomers' transitional phase was hardly explained in previous work.

With this in mind, the following sub-sections discuss the influence of the four institutional mechanisms involved in innovation generation in accordance with the conceptual framework and empirical analysis: a) investment policy, b) incentive and evaluation policy, c) industrialisation-related policy in each concerned ministry and d) the alignment of relevant policies.

[192] A few recent studies pointed out several institutional problems in fostering the biotechnology industry in Asian NIEs: top-down governmental leadership, loose coherence among innovation actors, lack of market incentive for innovation activities, and *Chaebol*-based biotechnological industrialisation (Dodgson et al. 2008, Hsieh and Lofgren 2009, Wong 2011). However, recent works identified only macro-level political and economic problems.

[193] While some recent studies focused on the linkage between universities and industries, they mostly remained in the macro-level quantitative analysis, rather than the in-depth analysis of the operational dynamics of the S&T policies (e.g., Eom and Lee 2010, Park and Leydesdorff 2010).

Table 8.1: Summary of institutional and organisational dynamics

Institutional and organisational factors		Influence on exploratory learning
Pharmaceutical SIS (Governance of S&T policies)	a) Investment	• Structural establishment of public and private innovation actors conducting exploratory learning • Active investment in exploratory learning in new biotechnological paradigm • Seed money style investment with dual effects on exploratory learning
	b) Incentive and evaluation	• Rapid accumulation in scientific research; publication • Establishment of formal channels for collaborative research between public and private actors • Inhibition of exploratory learning by short-termism of performance evaluation of national R&D projects • Low interaction between public and industrial actors • Institutional inertia towards risk-averse and short-term performance
	c) Industrialisation of science research	• Inter-ministerial compartmentalisation and lack of inter-ministerial coordination in R&D and industrialisation support; Support for new biotechnology by MOST and MOTIE, Support for synthetic drug-based pharmaceutical firms by MOHW
	d) Policy alignment	• Failure to align upstream and downstream incentives for mutually compatible exploratory learning • Mismatch between the product nature and division of R&D support by compartmentalised ministries
Firms' organisational mechanisms (Technological/ organisational)	g) R&D process	• Lack of active feedback between R&D teams • The overlooking of market needs in drug development
	h) R&D strategy	• Late rectification of the long time frame of exploratory learning to market • Late search for niche innovation pathway • Limitation in achieving economy of scale of R&D
	i) Organisational structure	• Function-based drug R&D • Delayed structural change in the R&D centre

	• Emergence of the arm's length R&D organisation
j) Top management	• Active support for exploratory learning by owners
k) Organisational code	• Exploitation-oriented organisational code

Source: Own elaboration

8.2.2 Investment policy

The structural establishment of competent innovation actors is the first institutional task needed to strengthen exploratory learning (Chapter 3, Sub-Section 3.3.2). Various public and private innovation actors must work together due to the industry's reliance on science and the fragmented nature of its knowledge base. The empirical evidence suggests that this precondition for enhancing exploratory learning has been met with the help of active governmental support.

8.2.2.1 Direction, manner and outcomes

Three aspects of national R&D investments to support technological innovation are examined here: the direction, manner of allocation, and outcomes of national R&D funding.

First, the majority of R&D funds were directed to upstream biotechnology research. It seems to be an effective R&D strategy for latecomers to aggressively move to an emerging technological paradigm (Chapter 2, Sub-section 2.3.1). The main driver of support for biotechnology was the national aim of compensating for the technological inferiority of the synthetic chemistry-based pharmaceutical industry by helping it adopt new technologies. Latecomers have relatively weak technological capability in dominant synthetic drugs. In contrast, they seem to have more opportunities in biotechnology due to the wide range of biotechnological drugs and their very early technological and market stage. A few studies and the present empirical cases show Asian latecomers' attempts to take advantage of emerging niche markets with different technological focuses, such as protein drugs and cell therapy in various therapeutic fields.[194]

The experiences of the US and Germany partly support Korea's investment in emerging biotechnologies as a latecomer. The US has taken a firm lead in bio-pharmaceutical innovation ahead of Germany over the last two decades because it actively fostered

[194] The movement of the other first-tier Asian NIEs, such as Taiwan and Singapore, towards biotechnology has already been noted (e.g. Dodgson et al. 2008). This implies that fast-following countries intend to use new technological opportunities as their next developmental engine and vehicle for taking over the market. They have relatively weak technological and systemic attachment to the dominant synthetic drugs.

biotechnology by supporting public research and a number of competent DBFs in the 1960s and 1970s (Collins 2004). Meanwhile, Germany, which led the synthetic drug-based pharmaceutical industry with its large chemical companies, struggled to establish a commercial base for emerging biotechnology during the 1980s and 1990s (Kaiser and Prange 2004). The systemic attachment to synthetic drugs by large chemical firms and their influence on R&D policy is seen as a main reason inhibiting Germany's rapid move to biotechnologies (*ibid.*).

Second, R&D funds were allocated on a small scale across the large number of innovation actors. The empirical evidence suggests that the small-scale distribution of funds contributed to establishing the initial capability for technological exploration. The 'seed money' style of investment helped build the overall knowledge base of various GRIs and universities. It also helped incumbent pharmaceutical companies engage in new-drug R&D by decreasing the initial risks of exploration. However, the empirical evidence suggests that this 'seed money' style of R&D support is having increasingly negative effects as the cost of companies' new- drug R&D intensifies and they need larger-scale support. These negative effects are connected to other policy factors and are discussed in the next sections.

Finally, the empirical results, at first glance, suggest that efforts to promote innovation actors' exploratory learning have been successful in terms of investment performance. The number of publications and patent applications rapidly increased under the new policy regime. However, up to this point in time, few R&D investments have been developed into commercially successful products. With this in mind, the following sub-sections discuss policies relating to the operational mechanisms of national R&D investment.

8.2.3 Incentive regime

The conceptual framework underscored the vital role of incentive policies in the successful promotion of exploratory leaning (Chapter 3, Sub-section 3.3.2). In essence, the empirical results showed that two institutions shaped the incentive regime of national R&D: the PBS, with its emphasis on publications, patents and products (3P), and S&T policy networks led by professors. The PBS acted as the fundamental incentive system for individual researchers, with some exceptions. The closed-policy networks led by civil servants and professors influenced the establishment of the national R&D agenda and the selection of innovation actors to participate in NRDPs. There were both positive and negative effects of the incentive regime in terms of meeting the two key dimensions of exploratory learning: the basic features and interactivity of learning. The basic features

consist of the intra-organisational aspect of exploratory learning (*RQ 1.1*), while interactivity involves an inter-organisational aspect (*RQ 1.2*).

8.2.3.1 Dual effects on exploratory learning

- Positive effects on exploratory learning

The incentive regime had a positive effect on the establishment of basic research capabilities and institutional arrangements for public and industry collaboration. First, the rapid increase in academic publications and patents was driven by the quantity-oriented evaluation of research performance under the PBS system. Without a prior knowledge accumulation of scientific research to some extent, latecomers are unable to advance towards an exploratory mode of technological learning. Due to the cumulative nature of science, a certain number of scientific experimental results is necessary to advance research in a new area, such as AIDS (Barbot 2002, referred to in Callon 2003, p. 62).[195] The PBS system was important in this respect.

The incentive regime also provided the institutional base for channelling public research and industrial R&D. The selection of NRDPs increasingly involved technological transfers and co-participation of public and private actors in R&D projects. As noted, this is an important institutional arrangement for funnelling innovation from public research to industrial development. This is due to the weak research and financial capabilities of industry in the latecomer context, and the fragmented nature of knowledge in a science-based industry.

- Negative effects on exploratory learning: intra-organisational aspect

However, the quantity-focused incentive regime partly counteracted the bold national investment in R&D. The emphasis on quantity interrupted both intra- and inter-organisational aspects of exploratory learning.

In terms of intra-organisation, the incentive regime failed to provide a stable and autonomous research environment for continuing exploratory learning in public research organisations. Evaluation criteria incentivised short-term performance based on the number of publications and patents produced. This led public innovation actors to avoid risk-taking and long-term exploratory learning. Under the annual quantity-based project evaluation, almost 95% of NRDPs were reported to be successful. Research teams

[195] Moreover, the science-based technologies/products of advanced countries have been increasingly protected by the patent system and thus latecomers' internal accumulation of scientific knowledge base has become critical in the industry.

tended to imitate each other due to the fear of failing to obtain future projects, and research topics were often decided by the possibility of receiving project funding.

- Negative effects on exploratory learning: inter-organisational aspect

The other dimension of exploratory learning, interactive learning, was also considerably disturbed under the incentive regime. The conceptual framework highlighted the fact that innovation requires dynamic interactions among innovation actors. However, in practice, publication-oriented incentives reduced this kind of practical collaboration.

First, in public research, organisations did not actively interact with each other because they competed for projects. Second, the industrial potential of research took a lower priority in GRIs and universities due to the short-term pressure to maximise the number of publications. DBFs, which found it difficult to continue business R&D under the weak venture capital system, relied heavily on NRDPs; they were set on publications being the main evaluation criterion for survival. In turn, pharmaceutical companies often lacked motivation to participate in joint NRDPs. While they sometimes formed consortia to apply for NRDPs, due to the requirement for joint applications, their interests were not aligned under the incentive regime.

Moreover, NRDPs run by professors cemented the attachment to publication-based incentives. Professors dominated the NRDP selection process. They were primarily interested in producing publications about emerging upstream research fields and issues, while the pharmaceutical industry tended to search for proven research outcomes for rapid industrial application. The former group was often attracted to leading-edge research topics in biotechnology, while the latter preferred to focus on methodologically proven synthetic drug-based R&D.

As a result, inter-organisational collaboration, the other critical feature of effective exploration, often remained at the superficial level of collaboration to acquire NRDPs. This study's micro-level qualitative analysis is consistent with recent macro-level quantitative studies on the collaboration between universities, GRIs and industry in Korea (e.g., Eom and Lee 2010, Park and Leydesdorff 2010). The studies suggest that changing the quantity-based evaluation system would promote interactive learning. They found that there were low rates of co-authorship across the organisations, even as the number of publications rapidly increased (Park and Leydesdorff 2010). In addition, Eom and Lee (2010) note that there is only a weak relationship between the rapid increase in the number of patents resulting from university and industry collaboration and firms' performance.

8.2.3.2 Institutional inertia in the incentive regime

Institutional inertia stemming from strong support for technological assimilation and improvement in the rapid catch-up stage is argued to be one of the underlying causes of the problematic incentive regime. This inertia leads to an over-emphasis on the short-term performance of technological learning.

In general, it can be said that fast followers, such as Asian NIEs, enjoy a latecomers' advantage by reversing the PLC. This reduces the amount of risk they face compared to forerunners.[196] Starting from a simple assembly of components, latecomers can gradually learn to design their own entire products. In the case of the major catch-up industries in Asian NIEs, their modular products further decreased the risk of such learning and led to the rapid conversion of learning into commercial profit. The high decomposability of modular products into components makes it easier to engage in stepwise technological learning, and to convert this learning to profit.

In these cases, the main risk of the latecomers' learning was reduced to how quickly they could master and improve existing products and technologies. That is, the probability of technological failure was inherently low, and the amount of time it took to learn was the key issue. Mission-oriented NRDPs, which were the most common type operating until the mid-1990s were effective in decreasing the time taken for learning. Hence, the evaluation of short-term learning performance was reasonable.

However, in the transitional phase, there was an increasing gap between the continued expectation for short-term performance and the rapidly changing knowledge dynamics. As seen in the empirical analysis, the main risk of learning was extended to include what and how to learn. Increasing the exploratory mode of learning thus became necessary, but this takes far more time. Moreover, a high project failure rate became inevitable due to an immature knowledge base of emerging sciences and discovery-oriented learning. However, the incentive regime lagged behind, still focusing on short-term performance; it was unable to accommodate long-term, high-risk research.

As a result, it can be said that the incentive regime negatively affected exploratory learning. It encouraged learning in some new high-tech areas of science, such as stem cell therapy. However, it continued to focus on understanding and validating emerging knowledge fields, rather than seeking new knowledge and opportunities. Out of concern that they would not receive research projects and funding, researchers avoided risk and

[196] The latecomers were able to gradually learn from the simple assembly of components to own design of the entire product by following the reversed PLC.

failure. In this case, defective exploratory learning was partly due to the out-dated institutional criteria for success; incentivising short-term performance was initially successful in promoting rapid catch-up, but was not helpful in facilitating exploratory learning during the transition.

Interestingly, aversion to risk and a short-term focus were not policy-specific flaws but common among innovation actors in the Korean innovation system. The empirical results showed that venture capital tends to evaluate the DBFs' R&D pipeline within a fairly short time, usually around three years. Five years was the longest period of investment. The results also showed the reluctance of *Chaebol* to undertake long-term investment in biotechnology-related R&D. Pharmaceutical firms started exploratory learning only when they recognised they needed to develop their own new drugs in order to survive.[197]

To sum up, the main problem with the incentive regime was its strong bias towards quantity-oriented, short-term performance. While such incentive regimes were effective in facilitating technological learning in the imitation stage, in the transitional phase they inhibited innovation actors' efforts to strengthen exploratory learning and further interrupted the smooth transition to a knowledge-generating SIS.

8.2.4 Industrialisation policy

The conceptual framework, for the effective industrialisation of scientific research emphasised the need for synergetic connections between research-oriented and business-based exploratory learning. This is fairly different from the ways in which technological learning took place during the imitation stage, when the focus was generally on exploitive learning. Thus, policies for industrial utilisation of technological learning rarely needed to consider the lengthy R&D process associated with upstream research.

Unlike the imitation stage, the transitional phase in the pharmaceutical industry requires the extension of policies for industrial utilisation of technological learning to cover upstream scientific research. This institutional change can be seen in the different

[197] Inertia associated with risk aversion is also observed in other Asian NIEs' biotechnology investment, although it is not directly related to the case of incentive systems. In the case of Singapore, they focused on investment in infrastructure and human resources to attract multinational companies (Wong 2011). This was the same development pattern of attracting multinational firms and placing them in the global production network as they used for the ICT industries (*ibid*). Thus, the risk of failure in fostering local innovation actors could be avoided (*ibid*).This is a kind of "survivalism" of Singapore as a small city state (Wong 2011, pp.165-189). In contrast, Taiwan is seen as having relatively risk-tolerant tendencies in its government support of biotechnology because of the SME-led national developmental trajectory, referred to as "many sprouts" (Wong 2011).

administrative patterns of the three leading ministries involved in R&D support and industrialisation of drug R&D: MOST, MOHW and MOTIE.

8.2.4.1 Policy pattern of the three ministries

This sub-section begins by summarising the diverse institutional motivations of the three leading ministries to join drug R&D support. It then discusses how the compartmentalised administration of S&T policies by each ministry interrupted connections between diverse innovation actors' technological learning. Note that interactivity has been argued to be a key condition for successful exploratory learning.

First, MOST ultimately aimed at strengthening scientific research capabilities (thereby leading to innovation) under the Biotechnology Promotion Act. The ministry strongly supported umbrella organisations, GRIs and universities. DBFs, as the commercial base for upstream research, were also supported by the ministry's various NRDPs.

However, the empirical results of this study showed other, unexpected effects of the interactive learning between industrial and public organisations. The dominance of public organisations, together with the incentive regime, the PBS-based incentives and the professor-led selection environment of NRDPs, turned the public actors' exploratory learning away from the needs of industrial actors. The results of public research tended to remain within their organisations, given the short-term, publication-oriented performance evaluation policy. As a result, the pharmaceutical firms' demands for commercially viable sources of innovation were largely unmet by NRDPs.

MOHW's R&D support was generally not used for industrial innovation, but to support the industry as a supplier of qualified generic drugs. This was to help ensure the stable management of the NHI. Thus, the funds were distributed through small-scale R&D projects to generic drug developers for encouraging process innovation.[198] One positive outcome of this was that there was direct R&D support for 'old' chemistry-based synthetic drugs, which currently dominate pharmaceutical markets. MOST, on the other hand, focused on supporting upstream new biotechnology research.

However, the empirical analysis revealed another perspective on the policy pattern in terms of exploratory learning. The increasing R&D support did not meet the changing demands of NRDPs, which included demands for larger-scale funding and more market-reflective R&D support. Although MOHW NRDPs continued to support new-drug R&D with small-scale funding (7.97% of the total R&D investment in 15 NCEs), support for

[198] The NRDPs embraced the bottom-up style projects often proposed by pharmaceutical firms.

new-drug R&D was not the focal area of the ministry. This is reflected in the recent dissatisfaction of MOHW's umbrella industrial association (KPMA) with new-drug R&D support (Chapter 5, Section 5.5.1).

More specifically, there was a lack of industrial policies concerned with industrial upgrading, although MOHW took charge as the juridical ministry of the pharmaceutical industry and hence was responsible for its industrial development.

The underlying reason was that the ministry did not have institutional experience in fostering an industry. It did not even attempt to foster the pharmaceutical industry until a few years ago. As a consequence, it can be said that MOHW has failed to embrace the movement of the KoPI towards new-drug development within the institutional framework of public health policy.[199]

MOTIE focused on the industrialisation of emerging biotechnology, launching a series of downstream-oriented NRDPs to foster DBFs and attract *Chaebol* to the emerging industrial area. The empirical results of this study illustrated the clear benefit of this policy to DBFs and a few *Chaebol*, which both benefited from MOTIE's active resource inputs.

However, the empirical evidence also revealed that MOTIE did not embrace exploratory learning by incumbent pharmaceutical firms. When it fostered an upstream research-based biotechnology industry, MOTIE overlooked the importance of the role of the incumbent pharmaceutical industry as a key commercial channel. There were two underlying reasons for this.

First, even for MOTIE, which was the key player in the series of industrial policies leading to the country's fast catch-up, the fostering of science-based industries was an unfamiliar policy challenge. The institutional unfamiliarity is particularly related to three policy spheres: technological learning, market creation and inter-actor relationships. In terms of technological learning, biotechnology industrialisation is based on a high degree of exploratory learning that starts from upstream science. In contrast, the industrial policies of MOTIE had mostly dealt with the downstream development and localisation of foreign technologies. In terms of the market, the market for biological drugs was not yet articulated, whereas markets in other catch-up industries were already established when

[199] The author does not disagree with the fundamental role of MOHW as the regulator of the public health sector. However, on the other hand, in terms of the sustainability of the semi-public industry, there must be a certain role as an institutional promoter of developing new drugs by the local companies for cheaper and effective new drugs for the people. Without the existence of local new drugs, the market dominance by a small number of Big Pharma firms will continue. Many developing countries are already facing many negative effects of this, such as high import costs, a lack of appropriate drugs for common local diseases and further deficit of the national health system.

Korean companies entered. In other catch-up industries, policies focused on the protection of the domestic market and penetration of the export market. In the case of biological drugs, the creation of initial market demand was critical. In terms of inter-actor relationships, innovation actors in the pharmaceutical industry were more diverse and horizontal, while MOTIE's industrial policies often focused on vertical organisation of industries led by *Chaebol*.

The second reason, as noted, was that the established pharmaceutical industry was seen as falling under the institutional power of MOHW. While MOTIE supported biotechnology-based new-drug R&D, the regulatory and approval policies were administered by MOHW. The support by MOTIE to infrastructure and new start-ups for biotechnology was not closely linked to the final commercial channel, that is, the incumbent pharmaceutical industry. Rather, biotechnology was treated as an independent industry rather than a new technological base for the pharmaceutical industry. As seen, the industrial association of biotechnology was administered by MOTIE, while the pharmaceutical association was administered by MOHW. In contrast, most other catch-up industries were fostered and regulated by the same ministry, which allowed them to achieve rapid technological learning.

8.2.4.2 Inter-ministerial compartmentalisation

The empirical results showed bureaucratic competition to expand their juridical scope and budget in the rapidly growing biotechnology and healthcare sectors (Chapter 5, Section 5.5.1). Based on the analysis, it is argued that the inter-ministerial compartmentalisation of policy implementation conflicted with the key characteristic of exploratory learning, that is, effective interaction. Specifically, the translation of exploratory learning into commercially viable innovation sources was disturbed by this administrative pattern. As shown above, the three ministries continuously launched their own NRDPs and other policies to support biotechnology and the pharmaceutical industry. However, they made little practical effort to arrange and connect the dispersed NRDPs to one another. The need for inter-ministerial coordination remained at the top level of the policy agenda.

One negative effect of this was to inhibit the transfer of the outcomes of NRDPs from upstream research to downstream development, as this would have required cutting across the three ministries' juridical scopes. In principle, the upstream research projects launched by MOST should have advanced to downstream development projects administered by MOTIE and MOHW. However, they encountered an institutional bottleneck. If a project received R&D funds from one ministry, there was a smaller

chance it would receive R&D support from the other ministries. This was because of the difficulty involved in assessing the performance of the projects (Interview 42 (K-Pharma)). Among seven NCEs developed by the case firms in the first round, only one drug received R&D support from two ministries (see Table 6.13). The other negative effect was overlapping investment. The results showed that 21 public institutes (mostly GRIs and universities) were conducting similar drug R&D projects.[200]

To sum up, the strong R&D investment on the part of the three ministries was counteracted by compartmentalisation of policy implementation. Each ministry had different policy goals for R&D support, and there was a very weak mechanism to coordinate between ministries. This inhibited the development of cohesive connections between the exploratory learning of different innovation actors, which is necessary for industrialisation based on scientific research.

8.2.5 Policy alignment

The final emphasis in the conceptual framework was on the alignment of heterogeneous institutions as a critical factor to facilitate exploratory learning in individual organisations, and joint exploratory learning between innovation actors. This was conceptualised in terms of the alignment of relevant policies to produce mutually compatible outcomes related to exploratory learning. The empirical data showed that latecomers' exploratory learning in the transitional phase was significantly influenced by the increasing intersection of emerging science and public health policies and the conventional industrial policy.

The following sections discuss two macro-level aspects of policy alignment that can affect innovation actors' exploratory learning: the alignment of incentive-related policies between public science and industrial R&D (Sub-section 8.2.5.1), and the inter-ministerial division of R&D support in dealing with science-based industries with integral product architecture (Sub-section 8.2.5.2).

8.2.5.1 Failure to align diverse incentives

It can be argued that effective exploratory learning was disturbed by the limited institutional capability to align the incentives of public research and industrial R&D. A key factor driving the successful commercialisation of pharmaceutical research is a

[200] Moreover, the administrative delay in the reapplication and selection of NRDPs was pointed out as a problem.

comprehensive incentive regime with both ‘push and pull’ (technology and demand) incentives (Daems et al. 2005, Hsieh and Löfgren 2009).

With regard to public research, the results of this study showed that push incentives were widely provided by MOST, focusing on upstream biotechnology research. PBS and the strong influence of professors on the selection mechanism of NRDPs made the incentive system revolve around upstream scientific research. For a latecomer, this may seem to be the right focus to make up for the limited science knowledge base necessary for industrial innovation. However, as highlighted above, there is a critical problem with this. The incentive regime forced public innovation actors to become excessively attached to scientific publications. DBFs, which must come into play to translate upstream research into downstream development, were also locked into publication. Downstream development became a second priority.

In contrast, the key market-side incentive for industrial R&D arose from developing first generic drugs, specifically not NCEs. The MOHW’s goal of stable management of NHI led pharmaceutical companies to focus on the technological exploitation of established synthetic technologies. A relatively high price was guaranteed to first generic drugs in the NHI’s drug reimbursement scheme, 81% of the price of the original drugs until 2008.[201] Given the small difference in economic return between first generic drugs and new drugs, few pharmaceutical firms were willing to take the high financial and technological risk of actively investing in new-drug R&D.

Note that during the successful industrial catch-up in Korea, both technological learning and market-side incentive/penalty policies were effectively aligned with each other. In this context, it might be thought that the misalignment of the (science) push and (market) pull incentives decelerated the rate of science-based transition by disturbing the emergence of mutually synergetic exploratory learning between upstream and downstream innovation actors. The pharmaceutical firms’ development focus became synthetic drugs, often focusing on generic drugs, while upstream research was concentrated on new biotechnology. In policy practice, as pointed out, the misalignment of incentive policies was also an issue of inter-ministerial misalignment, as a single industry was being administered from diverse institutional perspectives.

Interestingly, other Asian NIEs have shown similar limitations in aligning research incentives with downstream incentives. Hsieh and Löfgren (2009) suggests the need for

[201] This is a very recent move to lower generic drug prices in order to reduce NHI costs. The policy to decrease the cost of generic drugs seems to result in pressure to develop new drugs.

institutional comprehension of both the active support of upstream biotechnology research and a favourable pricing policy for new drugs (Hsieh and Löfgren 2009).

8.2.5.2 Product nature and inter-ministerial relationships

The other issue of policy alignment has to do with inter-ministerial coordination in dealing with science-based industries that have integral product architecture. The physical decomposition of a drug into subcomponents is difficult because of the high interdependence of product functions, such as safety and efficacy. As a result, the clear allocation of R&D tasks to innovation actors becomes relatively hard. The difficulty in clarifying the organisational boundaries of R&D tasks seems to result in an institutional challenge when the three ministries all attempt to support drug R&D.

In the case of modular product-based industries, the deliberate consideration of the product nature at the policy level was unnecessary. The development of new products could be supported by selecting specific R&D actors based on the physical decomposability of products into components or subsystems. This industrial R&D support was mainly led by MOTIE, while the applied research was supported mainly by MOST. There was relatively little institutional conflict or confusion between the ministries, and a series of modular products could be successfully developed by a public-private R&D consortium led by a single concerned ministry. For example, support from the Ministry of Information and Communication led to the development of a digital electronic switching system called TDX in 1982, and the first commercialisation of CDMA in 1996.

In contrast, in the case of integral products such as drugs, it is difficult to give the administrative leadership to one ministry due to the deep linkage of upstream research and downstream development, and the difficulty of physical decomposition. Thus, in theory, the concerned ministries should collaborate to provide consistent R&D support. However, as seen, this was not effectively dealt with in the case of the Korean pharmaceutical industry because of the compartmentalised structure of the relevant governmental ministries.[202] The empirical analysis implies that the present governmental structure might have caused inefficiencies in promoting joint exploratory learning in pharmaceutical R&D. The ambiguity of dividing R&D support into the juridical boundary of each ministry (particularly for an integral product) may be an underlying obstacle impeding the inter-ministerial division of R&D support and policy alignment.

[202] Moreover, several NRDPs launched by different ministries overlapped, which might have led to wasting R&D funds. These overlapping projects arose from the ministries' tendency to expand their juridical scope to cover new technology.

The nature of an integral product might require an integrated or highly coordinated R&D programme that embraces the long process from upstream research to downstream development. No studies dealing with this issue were found, at least within the literature on catch-up and science-based innovation among latecomers.

8.2.6 Overall findings of Research Question 1

Research Question 1 addresses the influence of the rearranged S&T policies on innovation actors' exploratory learning. It paid attention to whether and how effectively the policies facilitated exploratory learning in order to create new sources of innovation. A sub-question seeks to determine the impact of these policies on exploration within organisations (*RQ 1.1*). It addresses the effect of policy in promoting the basic features of exploratory learning, such as highly uncertain and long-term learning of ill-defined problems, from the intra-organisational perspective of technological learning. A second sub-question deals with the interactivity of exploratory learning between diverse innovation actors (*RQ 1.2*). This concentrates on the impact of policy on interactive learning between the public and industrial actors, paying attention to the nature of science-based innovation in the pharmaceutical industry.

With regard to *RQ 1.1*, the analysis ultimately argues that the operational mechanisms of reformed S&T policies both promoted and impeded exploratory learning in some ways.

There are two major ways in which the new policies had a positive impact on exploratory learning. First, there has been active national investment in the newly emerging biotechnological paradigm, and Korea has rapidly established necessary innovation actors able to engage in the exploratory mode of technological learning. Public organisations, such as GRIs and universities and new technological start-ups, became the main beneficiaries of investment in biotechnology. This allowed the country to accumulate a critical mass of knowledge, which is vital for further exploratory learning. The empirical evidence shows a rapid increase in scientific publication and patenting in biotechnology. Second, the pharmaceutical firms were able to lessen the initial risk of attempting a high degree of exploratory learning (that is, engaging in new-drug research) by joining NRDPs when they faced the new product patent system for the first time.

However, the S&T policies also undermined the generation of key characteristics of exploratory learning in innovation actors' real learning practices. The risk-tolerant and persistent nature of exploratory learning, which is critical in new-drug research, was largely ignored by the new incentive and evaluation system. This study's findings suggest that the underlying incentive regime favoured short-term, visible performance.

A few examples of this have been highlighted over the course of the analysis. One is the contrast between the rapid growth in the number of science publications and the low impact factor of these publications. In the same vein, there has been a rapid increase in patenting and vague commercial contributions, which is sometimes referred to as 'blind' patenting. Moreover, the NRDPs' success rate of 95% suggests a risk-avoiding tendency in learning practices. The findings further suggest that this risk-averse tendency is not confined to national R&D support but also relates to broader national and organisational inertia stemming from the pattern of technological learning in the rapid catching-up stage.

To sum up, the findings suggest that Korea has limited institutional capability to promote exploratory learning during the transitional phase, in particular in a fast-following developmental context. On one hand, the strong investment undertaken in the catch-up stage established necessary innovation actors for a (innovative) knowledge-generating pharmaceutical SIS. On the other hand, the rearranged S&T policies still emphasised short-term performance, which has constrained enhancement of real exploratory learning.

With regard to *RQ 1.2*, the empirical evidence and analysis reveal that the reformed S&T policies tended to interrupt joint exploratory learning between incumbent pharmaceutical firms and public research institutes and DBFs. In other words, under the new S&T policies, the interactive features of exploratory learning were not cross-fertilised between the upstream and downstream innovation actors. Three pieces of evidence support this argument.

The first relates to the direction of R&D investment and its lack of ability to connect the new biotechnology-oriented public actors and synthetic chemistry-based industrial actors. Government investment in biotechnology missed the critical role of incumbent pharmaceutical firms in commercialising upstream biotechnology research. Biotechnology was regarded as an independent sector from the old synthetic chemistry-based pharmaceutical industry rather than as a multi-purpose, generic technology. While the government focused on innovation based on new technology, the incumbent pharmaceutical firms focusing on synthetic drugs received a minimal level of governmental investment.

Second, the incentive regime had a negative effect on interactive learning between the public and industrial actors. In public organisations, the emphasis on short-term performance led researchers to concentrate on producing publications rather than searching for real innovation sources. It locked DBFs into the same publish-or-perish

evaluation system, because they heavily relied on national funds. At the same time, the pharmaceutical firms were demanding commercially viable innovation sources. As a consequence, the incentive regime surrounding the NRDPs, in the industry view, disturbed synergetic interactive learning between the public and the pharmaceutical industry.

Third, there was inter-ministerial misalignment of R&D support in science-based industries, in particular those that manufactured integral architecture-based products such as drugs. The findings revealed that the compartmentalised governmental structure and expansive nature of each ministry's juridical scope hindered the interconnection of diverse exploratory learning.[203] MOST and MOTIE focused on supporting biotechnology, which has an unarticulated market. In contrast, MOHW supported synthetic drug R&D for the stable management of NHI, not for an industrial upgrade. The ministries' policy goals and practices were misaligned. Moreover, the nature of an integral product made difficult to clearly divide R&D support between the concerned ministries.

Summing up, the findings suggest that S&T policies disrupted the formation of cohesive interactions between public and industrial actors, even as a high degree of interconnection was particularly necessary in the pharmaceutical industry due to the nature of drugs as integral products. The low levels of interaction in exploratory learning can be empirically characterised, in a broad sense, as a decoupled evolution of upstream biotechnology research and industrial R&D focusing on synthetic drugs.

8.3 Organisational Factors Influencing Exploratory Learning

This section discusses the firm-level intensification of exploratory learning from both technological and non-technological perspectives (RQ 2). The initiation and increase of new-drug R&D activity by some leading Korean pharmaceutical firms reveals latecomers' organisational mechanisms to enhance the exploratory mode of technological learning.

It first presents the applicability of the literature to the empirical findings (Sub-section 8.3.1). It then discusses four organisational perspectives on firms' exploratory learning, including R&D process and strategy, organisational structure and some minor factors (Sub-sections 8.3.2 to 8.3.5). Finally, the overall findings are presented (Sub-section 8.3.6).

[203] The expansive tendency of the governmental departments can also be interpreted as a case of Parkinson's law (1955) that explains the multiplication of subordinates in the public administration.

8.3.1 Literature and empirical findings

- Latecomers' exploratory learning in literature

The literature review suggested that the nature of technological learning becomes more exploratory as latecomer firms transition to developing novel and sophisticated products. Exploratory learning by latecomers is discussed in the literature on both catch-up and science-based innovation.

First, in the catch-up literature, two common drivers of catch-up were identified. One was the continuous enhancement of absorptive capacity to rapidly reverse the PLC. The other was the rapid translation of their intensified learning into market profits through participation in the global production network. This pattern of catch-up is often represented as the OEM-ODM-OBM model. Second, the literature review pointed out the features of the transitional phase – a less favourable competitive environment and institutions for latecomers, more direct competition with advanced rivals and increasing pressure to comply with global institutional standards such as TRIPS.

The review showed the literature's recent focus on catch-up, and its emphasis on the variety of technological paths for transition and the increasing need for firms and nations to develop a transition strategy. Three technological paths for transition can be conceptualised (Figure 2.2):

i) an emphasis on developing improved products that advance the reverse PLC
ii) an architectural differentiation of the product, entering just after fixing a dominant design
iii) a direct attempt to develop novel products prior to the establishment of a dominant design

The last two paths in particular indicate latecomers' exposure to direct competition against forerunning innovators. The issue of strategic capability deals with the dilemma of whether to build relationships with forerunners. Specifically, the choice between competition and collaboration received special focus in the literature.

The literature review also pointed out the discontinuous learning pattern and environment between the imitation and innovation stages in the science-based pharmaceutical industry. Specifically, it argued that the need for a broad and deep scientific knowledge base and access to emerging biotechnology capabilities require a high degree of exploratory learning for transition. Additionally, the integral product architecture of drugs heightens the interactive and interdependent features of exploratory learning. These two

points are unfamiliar in the knowledge dynamics of latecomers' previous technological learning during the imitative production stage.

In this regard, the literature review highlighted the need for radical change in latecomers' technological learning to a more exploratory mode that will allow them to engage in science-based catch-up.

• Latecomers' exploratory learning in empirical analysis

The empirical analysis showed both the applicability and the limitations of the previous literature. First, the overall catch-up paths of Korean pharmaceutical firms fit the stepwise catch-up model and the conceptualised technological path for transition. The empirical data showed that latecomer firms start technological learning through the imitative production of raw materials, that is, the localisation of APIs. They then engage in new-drug R&D in two ways, observed here. One is the development of better/best-in-class new drugs, which can be classified under architectural differentiation. The other is the development of first-in-class new drugs, which can be seen as new products for the world. Therefore, a kind of OEM-ODM-OBM model is applicable to the long-term evolution of the KoPI. Second, the case study firms' on-going struggles to profit from their exploratory learning suggests relatively higher technological and market barriers to transition than are found in most modular-product-based industries. Third, the latecomer firms' continuous attention to biological drugs supports the literature's focus on the opportunities latecomers can find in emerging technological paradigms, although no successful cases have been yet realised.

• Limitation of the literature in explaining the transition of Korean pharmaceutical firms

However, there is also a gap between the literature and the empirical results in understanding how latecomers enhance their exploratory learning, and in explaining the possibilities and limitations of the more complex innovation environment associated with the production of novel drugs. This gap is mainly due to the literature's focus on specific, remarkably successful cases of rapid catch-up. These cases involve a few modular products-based industries that operate in diverse market segments. In contrast, the pharmaceutical industry is basically divided into two polarised markets, off-patent generic drugs and patented new drugs, requiring a high degree of exploratory learning. Latecomers' catch-up in this kind of industry is hardly addressed in the existing research. Moreover, the literature on science-based innovation barely deals with latecomer firms' science-based catch-up.

Overall, exploratory learning in latecomer pharmaceutical firms has not been studied in-depth. The literature tends to limit itself to answering the following questions: Is the mismatch between the reinforcement of exploratory learning and overall commercial stagnation due to organisational problems? Is it just attributable to the natural process of learning-by-failure that novice innovators have to undergo?

Given these challenges, the following sub-sections discuss the four organisational mechanisms associated with firms' exploratory learning investigated in the empirical chapters: exploration practices in new-drug R&D (8.3.2), R&D strategy for new-drug development (8.3.3), organisational structure (8.3.4) and other organisational mechanisms such as top management and organisational code (8.3.5). Finally, Sub-section 8.3.6 summarises the overall findings.

8.3.2 Exploration practices in new-drug R&D

The conceptual framework interpreted new-drug R&D activities in terms of the actualisation of the new exploratory mode of technological learning. In particular, it emphasised the many simultaneous interactions that must occur among R&D actors over the course of the long R&D process from discovery to commercialisation. The framework also pointed out that enhancing the process of exploratory learning coincides with the need to unlearn previously established learning patterns associated with imitation. Overall, changing the direction, learning logic and habits of technological learning were considered key points for successful drug R&D practices. The empirical data showed a gradual change in the learning pattern of pharmaceutical firms over time. It also revealed that this change was a bumpy process of learning by failure and readjustment.

Two aspects of the R&D practices concerned with exploration are worth noting. First, the R&D teams did not practise a high degree of mutual interaction during the drug R&D process, which can be considered one of the main reasons for the slowdown and relative inefficiency of Korean firms' new-drug R&D. Second, their new-drug R&D failed to reflect market needs to a large extent; instead, the firms' exploratory learning tended to be conducted following an upstream research-push approach. The analysis pointed out that, until recently, most pharmaceutical companies carried out new-drug R&D without employing clinical doctors who would be able to capture the changing preferences of patients.[204]

[204] These two behavioural patterns of learning are discussed further in the following sub-sections on the organisational perspectives.

8.3.3 R&D strategy in the transitional phase

The conceptual framework emphasised the increasing importance of latecomers' strategic capability to cope with changing market and institutional environments. It should be noted that the science-based pharmaceutical industry operates under a polarised technological and market gap between novel and imitative drug markets. In line with this, strategic capability here refers to the profitability and sustainability of latecomers' exploratory learning. Profitability involves the commercial effectiveness of exploratory learning, that is, the smooth translation of new-drug R&D into market profit. Sustainability concerns the vulnerability of exploration, particularly in small latecomer firms.

The changing focal areas of R&D between the first and second rounds of new-drug development are associated with both profitability and sustainability. In the initial round, the case firms exclusively concentrated on antibiotics and anticancer drugs; the market in these areas was already well articulated, created by Big Pharma. In contrast, the second round was characterised by the diversification of R&D areas into four fields in each firm. The first field comprised therapeutic areas related to quality of life, referred to as QOL drugs, beyond the single focus on necessary drugs such as antibiotics. The second category involved the development of incrementally modified versions of original drugs, known as IMDs. The third class consisted of phytomedicines based on existing natural plants combined with local traditional knowledge of medicines. The fourth was the growth of biological drugs from purely imitative learning to more innovative and commercial R&D.

The following discussion explains how the latecomers' means of succeeding in the new-drug business differ from those of Big Pharma, thus indicating the need for an idiosyncratic pattern of technological exploration. Specifically, three aspects of latecomers' strategic capability are related to latecomers' success in exploratory learning: the time risk of learning (Sub-section 8.3.3.1), the pathway of learning (Sub-section 8.3.3.2), and the scale and sustainability of exploration (Sub-section 8.3.3.3).

8.3.3.1 Time-to-market of exploratory learning

The empirical analysis found that the long lead time associated with new-drug R&D, often taking over 10 years with considerable commercial uncertainty, posed a key difficulty for latecomers. In the first round of new-drug R&D, many firms had to endure a prolonged R&D period because of a lack of stable profit sources (except for generic drugs). The large numbers of commercial failures after the market launch of the new drugs further aggravated the difficulty of continuing expensive exploratory learning.

In this context, diversifying drug R&D into a few areas can be seen as an effort to differentiate exploratory learning, depending on the time-to-market associated with technological exploration. Phytomedicine R&D took about 5-8 years, shorter than that of NCEs. IMDs took even less time to develop, just 2-6 years, which allowed companies to extract profit more swiftly from technological learning.[205]

Thus, the diversified R&D areas reflect the recent strategic attempt to fill the gap of profit uncertainty between the 10-year period of NCE R&D and the short-term profit that is gained from generic drug production. The empirical data captured the increasing possibility of creating profits by differentiating exploratory learning based on the length of the learning cycle, although it is still too early to assert that this strategy has met with success.

In the literature, the issue of time at the firm level has largely dealt with the relationship between innovation speed and influencing factors, such as organisational processes and structures (Markman et al. 2005).[206] [207] In the latecomer context, Bell (2006) similarly pointed out the importance of the time of technological learning in addressing the catch-up of industrialising countries:

> Over what time period must the investments in particular kinds of learning be made? When will the returns be realised and over what time period? How does this vary between types of phases of learning? What circumstances might affect those time-scales? (p. 32)

While the preceding quote emphasises the overall importance of considering learning time, interestingly, the issue of learning time tends to be relatively less well considered in the literature on the catch-up of East Asian firms. The main focus in the literature is the 'entry strategy', and timing is addressed in terms of market entry as latecomers.

The relatively lower amount of attention given to learning time in the literature is partly due to the literature's focus on a few successfully caught-up, modular product-based industries. Modular products have a relatively short learning cycle, making it highly feasible for latecomers to gain an understanding of the overall design logic through reverse engineering. Components that latecomers are unable to develop internally within a short learning period can be purchased outside. Given these technological features,

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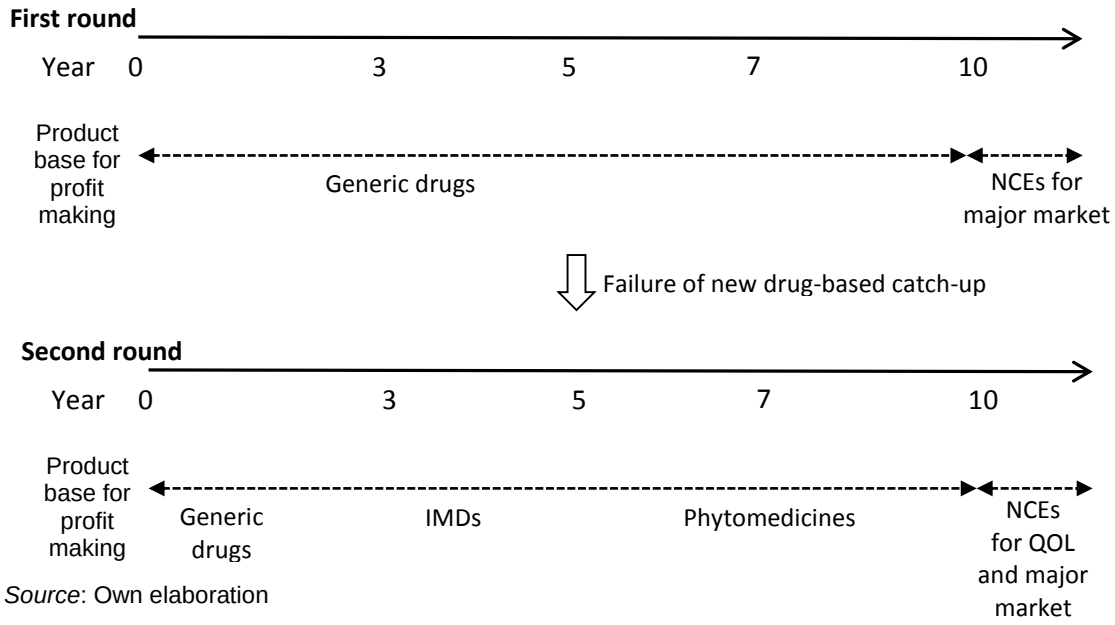
[205] The other side was to overcome the intensified competition of generic drugs and stringent IPR.
[206] It is based on the definition of innovation speed as the converting rate from discoveries to profit-making products (Stalk and Hout 1990).
[207] At the macro-level economic dimension, the time issue has been viewed in the diffusion rate of innovation such as new technologies (e.g., Kessler and Chakrabarti 1996).

concerns about the learning time can be managed to a large extent by strengthening the non-time factors of learning, and thereby speeding up the learning process. These factors include technology transfer, hard work, overseas training and crisis construction (e.g., Kim 1997a*,* Hobday 1998a).[208] Moreover, in Korea's case, the organisational advantage of a heavy investment in resources by virtue of the *Chaebol* structure also lightened the burden for firms in considering the time frame associated with learning.

For example, in a transitional phase, the matter of timing can be captured in a fast-follower strategy that focuses on swift entry into the early stage of a growing market with mass production capability. Samsung and LG entered the liquid crystal display (LCD) and secondary batteries (mainly lithium ion) business later than the Japanese original manufacturers (Sharp and Sony), but rapidly overtook them over the last decade. In the same vein, Samsung has successfully caught up with the first-moving Apple in the smart phone business. As for some core components that Samsung cannot develop yet, it is able to outsource these items to foreign suppliers and can, to some extent, skip the time-consuming part of learning.



Source: Own elaboration

Figure 8.1: Redirecting new-drug development

In contrast, the new drug business entails a much longer technological learning period. Design logic is difficult to master through reverse engineering; this only enables latecomers to master the synthetic process to produce generic drugs. Additionally, NCEs are protected by patents for about 10 years after market launch. Thus, it is difficult for

[208]Of course, we should not overlook the importance of previous knowledge bases and enhanced absorptive capacity.

latecomers to acquire good benchmark products that can guide the development process of new drugs. In turn, the learning time of latecomers becomes necessarily long, with a wider uncertainty gap between technological learning and profit creation.

Consequently, the present study points out that Korean latecoming pharmaceutical firms did not strategically consider the time frame of short-term, medium-term and long-lasting learning. However, the deployment of the R&D projects based on the time frame of exploratory learning was just as important for the latecomers as other time issues, such as the reduction of the development time of NCEs and the timing strategy for market entry (Figure 8.1).

8.3.3.2 The paths of exploratory learning

The difference in new-drug R&D between the first and second rounds reveals another area of strategic complexity surrounding latecomers' exploratory learning: the paths for transition. Specifically, the empirical data showed that there was a latecomer's dilemma in challenging the new-drug business in the first round, leading to an incremental reconfiguration using a strategic mix of competition and complementarity. This shows why it is important for each firm to develop specific catch-up paths, depending on its circumstances and internal resources (e.g., Lee and Lim 2001, Hobday et al. 2004, Hobday 2005, Wong and Quach 2006), and why it is useful to have a strategic mix (Hobday et al. 2004).[209] [210]

In the first-round of R&D, the latecomers encountered strong antecedent movers, that is, Big Pharma, directly competing against them in the early transitional phase. The case firms targeted primary disease markets that were already dominated by Big Pharma. They therefore had to compete with Big Pharma in the race for both new-drug R&D and marketing. However, for the global development and marketing of their new drug candidates, the local latecomers relied on Big Pharma. Most drugs transferred to Big Pharma turned out to be commercial failures. This isolated the local latecomers from the

[209] Basically, the effectiveness of forming specific catch-up paths by substituting for missing prerequisites was argued for by drawing on the late industrialisation of Germany (Gerschenkron 1965). Different paths of industrialisation taken by East Asian countries, such as Korea and Taiwan, and South East Asian countries, such as Singapore and Malaysia, were similarly exemplified to support Gerschenkron's perspective (Hobday 2003). Basically, the arguments stemmed from the fact that latecomers emerging after the antecedent industrialised countries have faced different external environments, internal resources, knowledge bases and institutions. While the formulation of catch-up paths at the national level has received relatively more attention, often in inter-country comparisons (e.g., Gerschenkron 1965, Hobday 2003, 2011, Rodrik 2008, 2010), that of the catch-up path at the firm level seems to remain in a conceptualising stage (Hobday et al. 2004, Hobday 2005).

[210] This was pointed out in the context of the strategic complexity and increasing need for dynamic capability of the catch-up in the transitional phase (Chapter 2, Sub-section 2.3.1.2).

global market due to the loss of the then almost singular marketing channel for exporting their own new drugs.[211]

There are few historical instances in which an industry has caught up by exploiting only the domestic market. Participation in the global production network (Ernst 1997, Ernst and Kim 2002) is necessary for stepwise catch-up due to weak local demand for high-cost novel products until a certain income level. Therefore, detachment from the global market implies the failure of market catch-up for most latecomer countries.

In contrast, the diversification of R&D areas in the second round signifies the possibility of solving the latecomers' dilemma, that is, the blind dependence of the new-drug business on Big Pharma. The newly diversified R&D fields can be regarded as an expression of the dual strategy of complementarity with and competition against Big Pharma. The complementary strategy is performed by specialising in developing new drugs in relatively small niche markets. Big Pharma is rarely willing to be directly involved with such small markets. For latecomers, this R&D path offers a higher possibility of supplying innovation sources to Big Pharma. At the same time, the competition strategy is attempted by continuing R&D in the primary disease areas with a diverse array of drugs, such as NCEs, phytomedicines and IMDs.

The industry's small successes in supplying IMDs and transferring QOL-oriented drug candidates to Big Pharma for global marketing, as well as the domestic competition against Big Pharma in phytomedicines and QOL drugs, suggests the potential effectiveness of a strategic mix. In other words, the KoPI is competitive in the domestic market, but complementary in terms of global development.

The following comments by the CTO of Dong-a (Interview 48) explain the strategic change in the latecomers' new-drug-based catch-up from single-mode competition in a major market to complementary competition in niche markets:

> In our long experience of trial and error in the new drug business, including the recent success of Zydena [a QOL drug], we came to realise that specialising in a few niche therapeutic areas in developing new drugs such as Actellion and Gilead[212] and their transfer to Big Pharma after the II/a clinical trial is the most realistic way of survival and growth for Korean companies. … In brief, we refer to

[211] For Big Pharma, the renunciation of further development of in-licensed drug candidates is regarded as a strategic option as latecomers operate substitutable drug candidates in general.
[212] Actellion specialised in pulmonary arterial hypertension. Gilead was the original developer of Hepsera and Tamiflu.

> the new strategy as the '2A model in the specialised QOL areas' ... Moreover, we also captured market opportunity in East Asia through phytomedicine R&D based on our similar culture of traditional Oriental medicines. … We refer to this as a 'semi-globalisation' strategy.

Overall, the analysis suggests that the key to latecomers' dual strategy is to concentrate on exploratory learning by considering the weaknesses of the dominant players' product portfolio, both complementarily and competitively. From a stepwise catch-up perspective, the complementary strategy can be perceived as an ODM strategy for the global market, while the competitive strategy is an OBM strategy focusing on local and emerging markets.

8.3.3.3 The scale of exploratory learning

The last strategic perspective on the commercial effectiveness of exploratory learning involves its scale. It is closely related to the issue of the reduction of development lead time mentioned above. The empirical data showed frequent delays in the timely market launch of domestic firms' new drugs. Regardless of the other external factors such as the relationship with Big Pharma, one fundamental reason for prolonging the development time was the limited availability of resources for an intense investment in each new drug project, unlike Big Pharma.

While new drug discovery has a highly explorative nature, it also has labour-intensive features. The more researchers there are who can be involved in upstream research and synthetic experiments, the higher the possibility of discovering the right drug candidates within a shorter time frame in general. As a *Chaebol* affiliate, LGLS showed better investment capability than other case firms. For most case firms with a small number of researchers (200-300 on average), the drag of the development lead time is likely unavoidable, leading to exposure to more uncertainty and market change. The scale aspect of exploratory learning made the KoPI very different from other catch-up cases in industries driven by *Chaebol*.

8.3.4 Organisational mechanism

Turning to the organisational aspects of technological learning, the conceptual framework pointed out the importance of the organisational structure in promoting the key characteristics of exploration. There are two key aspects of the organisational structure in terms of its impact on exploratory learning: its influence on the interactive feature of exploration (Sub-section 8.3.4.1) and the sustainability of exploration (Sub-section 8.3.4.2).

8.3.4.1 Delay in changing R&D organisational structure

The empirical data showed that in the first round and at the beginning of the second round, new drugs were developed under a function-based organisational structure. In the imitation stage, a function-based team structure worked well because the goal and content of technological learning were well defined. The division of R&D tasks was clear, eliminating the necessity for a high level of interaction. A synthetic team would only need a minimum level of feedback from a safety and efficacy testing team, because it was working on already validated drugs. Each team's mechanistic concentration on its given learning tasks per team was critical for the rapid mastery of the imitative development process.

However, the empirical findings showed that this function-based organisational structure is inefficient for new-drug R&D. Specifically, the function-based R&D teams had structural limitations in moving between the repeated synthesis of chemical compounds and the subsequent biological tests for toxicity and safety. Because of the explorative trials necessary to identify potential drug candidates, continuous feedback between the R&D teams, including the marketing department, was critical (Interviews 48 and 51 (K-Pharma)).

After the commercial failure of the first new drugs, firms began to reorganise for the second round of R&D. This included the reorganisation of R&D centres from a function-based to a product/project/matrix-based structure. The reconfiguration also created research evaluation committees consisting of medical doctors and team leaders from various upstream and downstream functions.[213] Moreover, the case firms also tried to recruit Korean senior researchers who had experience in new-drug development in Big Pharma.

These changes imply that firms recognised the differences in organisational structure between exploitive and exploratory learning. A product/project/matrix-based organisational structure seems to have a stronger affinity with the interactive nature of exploratory learning than does a function-based structure.

In general, it is difficult to devise an optimal intra-organisational structure for exploratory learning. However, the literature on project management suggests that interactive and flexible learning is easier with project/product/matrix-based organisational structures than with a strictly divided function-based team (e.g., Galbraith 1971, 1974, Ford and

[213] For example, drug identification, preclinical development, clinical development and marketing.

Randolph 1992, Hobday 2000, Sydow et al. 2004).[214] Particularly, the literature shows that organisational structure tends to evolve from a function-based hierarchy to a project-based framework, then to a matrix-based structure that deals with the changing environment (Ford and Randolph 1992).

In line with this, the matrix-based structure can be seen as an effective organisational structure for new-drug R&D. This argument is partly supported by organisational reforms in a few Big Pharma firms. In the late 1990s and early 2000s, Swiss-based Novartis and Roche changed their R&D organisation from a hierarchical function base to a cross-functional project/matrix base (Zeller 2002). This approach was aimed at integrating the various R&D functions and decision-making processes, thereby speeding up the development process (*ibid.*).[215] The results of Biopartnering Survey (IBM Institute 2010) presented a similar viewpoint, indicating that collaborative R&D can be better promoted by a therapeutic-based than a fixed-function-based organisation. Here, 'therapeutic-based' can be seen as the equivalent of 'product-based' in the pharmaceutical industry.

Overall, the literature reports that there are many positive attributes of a matrix/product-based organisation for interactive learning. It also notes that the influence of organisational structure on exploratory learning, at least in terms of interactivity, is commonly applicable to latecomers, although these studies have tended to focus on globally networked, large-scale R&D organisations. The empirical analysis showed a delayed change in the organisational structure as the passive response to failure or a lag of exploratory learning in creating market profit.

8.3.4.2 The arm's-length R&D organisation

The conceptual framework highlighted the fact that that the autonomy of an R&D organisation is necessary for sustaining exploratory learning. It is based on the mutual exclusivity between exploitation and exploration, given a firm's limited resources. A common architectural solution offered in the literature is to operate a decentralised R&D organisation for exploration. This is ultimately aimed at avoiding potential conflicts and tensions between the two modes of learning.[216]

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[214] Although this discussion focuses on the reason for the organisational change from the function base to the project/product base in latecomer firms, the literature on project management originally covered the difficulty of operating the matrix/project organisation because of dual control systems and resource allocations.

[215] The decreasing productivity in new drug development, compared to the case of US rivals, underlay the organisational change (Zeller 2002).

[216] For example, the latecoming Seiko operated an autonomous R&D organisation for learning the emerging technology of quartz movement and overtook the mechanics-based SSIH, a then-dominant Swiss watch company (Benner and Tushman 2003). Meanwhile, SSIH was attached to the dominant market share based on the old technology, although they kept learning the new one (*ibid*).

However, in contrast to the literature's focus on the ambidexterity of large or technologically advanced companies (e.g., Celltech by McNamara and Baden-Fuller 1999, Seiko by Benner and Tushman 2003), the case firms were small- and medium-sized, technologically inferior latecomers. The empirical data showed that as small-sized latecomers, they had insufficient resources to operate independent R&D organisations devoted solely to technological exploration. Moreover, an independent R&D organisation would seemingly be unnecessary for long-term exploratory learning because the firms' R&D organisation remained small and was thus easier to manage.

However, the empirical analysis found that there was an arm's-length R&D organisation played a positive role in sustaining long-term exploratory learning in small latecomer firms. This finding is supported by the experiences of two case firms. One is Mogam Biotechnology Research Institute, a public entity funded by GC. The other is C&C Research Laboratories, a drug discovery-oriented joint venture between JW and the Japanese company Chugai. Both R&D organisations have continuously supplied potential drug candidates or the upstream knowledge to their funding companies. Dong-a's recent reallocation of innovative drug research to its holding company also seems to support the argument in favour of autonomous, exploration-oriented research units. The holding company is not directly involved in the marketing activities for drugs.

After the commercial failure of its first NCE, LGLS reorganised its R&D, including the generic drug business. Similarly, Yuhan experienced a pipeline gap when it faced sales lags of its first NCE and thus restructured its new-drug R&D business. These cases indicate that latecomers also need a stable organisational base to provide potential drug candidates.

The experiences of some *Chaebols* are more vivid. Their attempts at biotechnology R&D were often disrupted by internal conflict and external shock, such as managerial pressure over the lack of profit generation after a few years of exploration and the Asian economic crisis in 1997. As a result, most Korean *Chaebols* that started biotechnology R&D in the late 1980s and 1990s gave up exploratory learning. Some of them, such as Hanwha and Samsung, are currently seeking to re-enter the biotechnology business through imitative learning associated with the development of biosimilar drugs.

In this context, the empirical analysis suggests the potential of an arm's-length, autonomous R&D organisation to preserve latecomers' sustainable exploratory learning, free from internal and external managerial risks. This is particularly true in science-based industries that are fed by long-running but highly uncertain technological learning. The

CTO of Green Cross referred to the Mogam Biotechnology Research Institute as a ‘reservoir of mid- and long-term technology’ for future profits and slumps.

8.3.4.3 Role of top management and ownership

Two other organisational mechanisms were also considered in the conceptual framework as influential elements of latecomers’ exploratory learning: the role of top management in initiating and sustaining exploratory learning and the effect of the organisational code on efficient exploratory learning. Both perspectives were partly traced throughout the firm-level analysis of Chapters 6 and 7.

The empirical data showed that family-based ownership and the family’s direct participation in management across generations are common in the KoPI, including in most case firms. There are both positive and negative effects of strong ownership on exploratory learning.

On one hand, company owners (often CEOs in the case firms) played an active role in sustaining exploratory learning. For example, the continuous long-term, new-drug development projects by LGLS, Dong-a and Ilyang were driven by the owners’ strong willingness to remain engaged. The analysis showed that the latecomers would have been unable to continue the long-lasting new drug projects without the owners’ support. This observation confirmed the findings of studies that have argued for senior management to play critical role in guiding the direction between incremental and radical innovation activities, and resolving the tension between the two modes of learning (e.g.,Tushman et al. 1997, Benner and Tushman 2003). On the other hand, strong ownership and its leading role in management seemed to inhibit joint exploratory learning among firms. The interviewees often pointed out the strong tendency to secure ownership as one of the critical barriers to inter-firm R&D, even though most owners realised the need for collaboration among small-sized latecomers.

Overall, it can be said that an instinct for survival and a strong sense of ownership among family owners underpinned the increasing support for exploratory learning within the firms. However, such strong attachment to family-based ownership also caused a lag in industry-wide exploratory learning.

8.3.4.4 The latecomers’ organisational code

The conceptual framework pointed out that an imitation-oriented organisational code can influence exploration-oriented R&D by individual researchers. Although this issue was not dealt with in the empirical chapters, the individual-level mechanism of exploration undoubtedly affects the efficiency of organisational learning.

Prior to starting new-drug R&D, the case firms and their researchers mainly engaged in reverse engineering for the imitative production of original drugs with little technological risk. The researchers were accustomed to single-mode learning, that is, exploitation. The empirical data showed the difficulty of the smooth conversion of behavioural patterns between exploitation- and exploration-routinised researchers. Researchers conducting generic drug development were mostly concerned with timing so that they could launch ahead of their rivals, as they were working in a field with low technological risk and uncertainty. In contrast, researchers implementing new-drug R&D were faced with higher technological uncertainty. The timing strategy for the swift market entry was of relatively little concern for the latter type of researcher.

In this regard, a few senior-level researchers pointed out that researchers in most Korean firms were still predominantly coded by imitative and risk-averse mind-sets. This situation caused inefficiency in exploration-driven new-drug R&D. Kale (2005) similarly captured the importance of an organisational routine coded to individuals in Indian latecomer firms' R&D. In his study, the difficulty of switching from an imitative to innovative mind-set was revealed when generic researchers tried to switch to new-drug R&D. Below is an observation from the head of new-drug discovery in a leading Indian firm, Lupin:

> There is this scientist; he was head of one group of the generic people. So I tried this scientist for eight months in new drug discovery, he couldn't ... deliver anything to me. Finally I have to ask him to please go back to generics now. This is my personal experience; with reverse-engineering experienced scientists, it is difficult (Kale 2005).

Similarly, the following two examples reveal the individual-level differences between exploitive and exploratory learning and the importance of organisational receptivity to these differences.

The first example shows the difficulty of switching between exploratory and exploitive modes of learning. When LGLS failed in marketing its first NCE, Factive, it set up a branded generic (BG) team in its R&D centre to focus on short-term profit. For the generic drug market, launching generics at the correct, earliest possible by evading patents is the most important factor in competing in this kind of market. However, the company underestimated the uniqueness of the technological and approval activities of the generic drug business (Interview 38 (Big Pharma).[217] The researchers at LGLS had little experience and related developmental knowhow in the time-sensitive generic drug

[217] Interview: a former researcher at LGLS.

business. They had accumulated knowledge and knowhow in technological exploration for a long time, but were unfamiliar with technological exploitation. That is, the 'core competence of developing new drugs and generic drugs were different' (Interview 36 (DBF)). As a result, the company's generic drug business has shown little competitiveness.

The second example shows the changing pattern of technological learning towards 'real' exploration (acquired from Donga Science, 08/03/2010). In 2006, a team from LGLS identified by chance a new chemical entity named Cytopro. When the research team led by Dr Sun-ha Kim tested the hepatotoxicity of a drug candidate for diabetes, they originally expected to see rapid necrosis as the candidate material increased. However, the result showed the opposite phenomenon. The measuring instrument reported an increase in the number of cells from 100 to 140. The researcher who conducted the experiment assumed that there was a defect in the measuring instrument; he was focused on the experiment's original goal. However, the team leader, Dr Kim, noticed that the cells involved in the experiment had become more active and healthy; he decided to redirect the experiment to test the effectiveness of Cytopro in protecting cells from necrosis. The team examined the mechanism of necrosis inhibition and then confirmed Cytopro's potential as a protective material for cells that can prevent necrosis.

Although this seems to be an example of a normal change in an experiment, it should be noted that the discovery was only made possible when the experimenters changed the way they thought and communicated with each other. As the former CEO of LGLS (Dr Incheol Kim) commented, the discovery of Cytopro meant failure of the researchers' past research pattern (or goal-oriented organisational routine) of implementing experiments, as it yielded a result contrary to their expectations: 'This drug would have been discarded if the same event had occurred in the past'.[218] Cytopro is now believed to be the only material that can protect cells from necrosis with commercial potential.

Overall, despite its accidental discovery, the recognition of Cytopro as a valuable material was driven by an emerging exploratory mode of learning. The research team started to reconceptualise the problem by reversing the known relationship between cause and effect. This signified an attempt to overcome mission-oriented, linear problem-solving activity.

[218] Similarly, the erectile function of Viagra was identified when Pfizer was implementing clinical trials for a cardiovascular drug.

To sum up, the analysis suggests that the exploitation-oriented organisational code was an underlying barrier hampering the smooth conversion to exploratory learning in latecomer firms. However, it also shows the possibility of a change of learning pattern to exploration.

8.3.5 Overall findings of Research Question 2

Research Question 2 is concerned with how effectively latecomers performed exploratory learning, which is the key mode of technological learning for new-drug development. Two sub-research questions were formulated by focusing on two aspects of exploratory learning: R&D practices, including the real drug R&D process and strategy (*RQ 2.1*), and the organisational perspectives that correspond to these R&D practices, such as organisational structure (*R.Q 2.2*).

The empirical analysis was conducted by reviewing 25 years of attempts to develop new drugs by nine local pharmaceutical firms. The first round of new-drug R&D was initiated by the reinforcement of the product patent system in 1987, a precursor of TRIPS. The second round was performed after 2000, when NHI reform led to a change in market structure and competition. The analytical dimensions were developed from the drug development practices and organisational processes.

Regarding *RQ 2.1*, the analysis concluded that latecomer firms had long struggled with building a virtuous cycle of the exploratory mode of technological learning and profit creation. New-drug R&D is characterised as the initial failure of profit extraction from first-round drug R&D, and a reconfiguring process in the second round. Three underlying reasons for this transitional pattern were laid out from the perspectives of R&D practices and strategy.

The first relates to the initial failure of managing the time frame of new-drug R&D to profit creation. Most case firms put an early focus on developing NCEs, which took 10-15 years. This led them to struggle to acquire stable profit sources. On the other hand, the analysis also found that more recently, the time scale of exploratory learning has been at the forefront of strategic considerations. New drug projects were deployed over three different time windows: short- (less than 5 years), mid- (5-8 years) and long-term learning (10 years). This was the outcome of concern with the payback point of the R&D investment.

The second reason is that R&D paths changed from single-mode direct competition to dual-mode complementary competition with the first movers. In the first round, the

latecomers blindly replicated Big Pharma's innovation model, the development of NCEs in major markets, such as antibiotics and anticancer drugs. The data revealed that the main problem of this innovation path was encountering direct competition with Big Pharma, leading to a decrease in commercial possibilities. In contrast, emerging alternative paths in the second round aimed to avoid direct competition with the market dominator by searching for niche markets. Case firms explored three paths of innovation, IMDs, phytomedicines and QOL-oriented NCEs, in parallel with biotechnology R&D. The biotechnology path aimed to seize opportunities for latecomers by quickly exploiting a new technological paradigm.

The third indication is the low intensity of exploratory learning in terms of investment scale. Most case firms, as small-sized latecomers, found it difficult to engage in exploration at the scale that was needed. They could not afford to allot sufficient resources to drug discovery in a timely manner and to actively take the risk of intense investment. As a result, the period of exploratory learning was prolonged and their pipeline drugs often fell behind those of competitors.

Overall, the findings suggest a weakness in latecomers' exploratory learning due to procedural and strategic errors in three aspects of technological learning concerning the speed of transition. The recent change implies that firms are continuously rectifying their learning patterns by considering strategic elements of exploration.

For *RQ 2.2*, the analysis concluded that the case firms' exploratory learning was performed under imitation-routinised organisational mechanisms, causing inefficiency in exploration practices. Three findings support this argument.

The first finding relates to the difficulty in actualising the key conditions of exploration in latecomers' real R&D practice, even when new-drug R&D itself is strongly supported by the top management. The literature review pointed out that a high degree of interactive learning is necessary for exploratory learning in science-intensive, integral architecture-based drug R&D. However, the empirical data revealed a low level of interaction among R&D teams and the absence of the demand consideration in their technology-push-style new-drug R&D.

The second piece of evidence involves the late restructuring of the R&D organisation as an underlying cause of the first point, that is, the defective R&D. The case firms' new-drug R&D was conducted under the then on-going influence of a function-based organisational structure, which was established at the imitative learning stage. The close interaction and rapid feedback among various concerned teams including R&D and

marketing parts were interrupted in the function-based organisation. The firms did not adopt more exploration-favourable structures, such as a product/project/matrix-based organisation, at a full scale until the late 2000s.

The third fact concerns the negative influence of the researchers' risk-averse and imitation-oriented mind-set on the firms' exploratory learning to develop new drugs. The researchers' imitative habit originated from the latecomer firms' focus on reverse engineering at the imitation stage. The data indicated that this approach is still influential in current exploration practices.

Overall, the findings confirmed that the case firms' reconfiguration of organisational mechanisms to promote exploratory learning was relatively delayed. Their imitation-favourable organisational routines disturbed the exploratory mode of technological learning. However, it should also be noted that the firms were gradually modifying their organisational mechanisms in a more exploration-friendly way, and were particularly concerned with the interactivity, business potential and sustainability of exploration.

8.4 Summary

This chapter answered the research questions concerning the factors that determine the enhancement of the exploratory mode of technological learning and ultimately influence the rate of the transition of the KoPI towards science-based industry. The institutional and organisational factors in the transition were discussed by comparing the study's empirical findings with the key characteristics and conditions of exploratory learning, such as its high-risk, long-running and interactive nature.

First, the institutional factors that influence innovation actors' exploratory learning were determined in terms of the effectiveness of the three policy categories and their alignment perspective in promoting exploratory learning. These categories consist of the investment policy, the incentive regime and the administrative pattern of R&D support by the three concerned ministries.

The discussion concluded that these institutional factors have both positive and negative effects on exploratory learning. The positive effects of the investment policy and incentive regime included the structural establishment of the necessary public and private innovation actors for enhancing exploratory learning and the rapid accumulation of knowledge stock in scientific research, particularly in the emerging field of biotechnology. However, under the quantity-based performance criteria and compartmentalised R&D support of the three involved ministries (MOST, MOHW and MOTIE), there were

interruptions in conducting individual and joint exploratory learning between the public and industrial R&D organisations. The discussion also argued that institutional inertia, short-term performance orientation and the integral product architecture of drugs underlie the poor implementation of the reformed S&T policies.

Second, the latecomer firms' pattern of exploratory learning was examined by focusing on the effectiveness of various technological and organisational factors in generating the key characteristics of exploratory learning. The thesis examined four technological factors – R&D practice, R&D strategy including the time frame and paths of exploration, and the intensity of the exploration – and three organisational factors – organisational structure, the role of top management and individual researchers' mind-set.

Based on the findings, the latecomer firms' new-drug R&D was finally characterised as an initial failure and its later reconfiguration to build a virtuous cycle of exploratory learning and market profitability. The first round of new-drug R&D involved the replication of established innovation models, focusing on the development of NCEs in major market segments. It failed to achieve market catch-up with Big Pharma. The second round was characterised by the search for alternative-niche innovation opportunities; companies diversified exploratory learning based on the strategic factors identified above. They tended to focus on four paths of exploration: IMDs, phytomedicines, QOL-oriented NCEs and biological drug R&D. A complementary competition strategy and an arm's-length R&D organisation can be an effective and strategic means of heightening the profitability and sustainability of latecomers' exploratory learning.

Chapter 9: Conclusion

9.1 Introduction

This thesis set out to explore the 25-year transitional process of the KoPI, from its initial focus on the imitative production of generic drugs to its own development of new drugs. The thesis was motivated by curiosity about the pace of catch-up in the science-based pharmaceutical industry, particularly in the development context of fast-following Asian NIEs. Unlike most successful catch-up industries, such as electronics and ICTs, which catch up within a relatively short period of development, the pharmaceutical industry seemed to achieve only modest catch-up performance after entering the transitional phase in the late 1980s.

The thesis was underpinned by four theoretical and contextual bodies of literature. First, the different styles of organisational learning, exploitation and exploration were employed to understand technological learning in the transitional phase. Second, the literature on innovation systems provided insight into institutional and interactive perspectives of technological learning. Third, the contextual literature on the fast followers' catch-ups and transitions was used to understand the developmental context of Asian NIEs. Fourth, the literature on the sectoral knowledge dynamics of the pharmaceutical industry was reviewed, focusing on the science base of drugs and their integral product architecture.

The literature review recalled the critical role of institutional and organisational mechanisms in strengthening exploratory learning as the key mode of technological learning for transition. In line with this, it further determined the key characteristics of exploratory learning in the science-based pharmaceutical industry, such as its high-risk, long-term and densely interactive nature.

The thesis finally argued that the rate of transition of the KoPI was affected by the degree of promotion of exploratory learning by institutional and organisational mechanisms. It also noted that the institutional and organisational promotion of exploratory learning is related to a 'pattern change' in the previously established institutional and organisational routines associated with imitative learning of existing technologies and products.

The argument and empirical analysis were theoretically based on a conceptual framework that viewed the transitional phase as a transformational process associated with certain institutional and organisational mechanisms. The key institutional focus in

this framework was the influence of revised S&T policies on the exploratory learning of innovation actors. The organisational transformation was investigated from the point of view of firms' increasing exploration in new-drug development.

The multidimensional investigation provided a broad picture of fast-following countries' bumpy transition process in the science-based pharmaceutical industry. It did not measure the exact speed of the transition of the KoPI or assess the success or failure of the transition. Rather, it uncovered a pattern of institutional and organisational factors that might have influenced the transition.

In terms of institutional factors, the study discussed the two-sided effects of the fast followers' STI policies on the innovation actors' exploratory learning. In terms of organisational factors, it revealed not only the latecomer firms' strategic awkwardness and organisational errors, but also the emerging potential to rectify these problems by focusing on niche markets. Synthesising these facts, it characterised the present transition rate as the combined outcomes of distorted exploratory learning on the part of public and private innovation actors and the lag in building a virtuous cycle of exploratory learning and profit creation. It can be argued that if the KoPI dealt more proficiently with these institutional and organisational factors, exploratory learning would be more efficient and the transition speed would be faster.

This final chapter first recapitulates the main findings (Section 9.2) and presents the theoretical contributions of the thesis (Section 9.3). Some implications of the research for policy and management are then suggested (Section 9.4), followed by a discussion of the limitations of the thesis and recommendations for future research (Section 9.5). Some closing remarks conclude the chapter and the thesis (Section 9.6).

9.2 Empirical Findings

The empirical findings were based on an investigation of the distinctive transitional dynamics of the science-based pharmaceutical industry, which produces integral products and is confronting an emerging biotechnological paradigm. The findings were discussed in four chapters: the technological, market and institutional context of the deepening transitional phase of the KoPI (Chapter 4), S&T policy reform and its influence on exploratory learning (Chapter 5), the evolution of new-drug R&D among latecomer firms (Chapter 6) and the corresponding organisational reconfiguration of such firms (Chapter 7).

In line with the research objective and research questions, the findings will be summarised along three lines: the specifics of the transitional phase in the science-based pharmaceutical industry (Sub-section 9.2.1), the institutional mechanisms' influence on the exploratory mode of technological learning (Sub-section 9.2.2) and the organisational mechanisms' impact on exploratory learning (Sub-section 9.2.3).

9.2.1 Transition in the science-based pharmaceutical industry

This thesis contended that the industrial transition from the imitation to the innovation stage requires not only an incremental accumulation of knowledge, but also changes in institutional conditions and organisational mechanisms. This is referred to as 'pattern change' and 'qualitative transformation'. Specifically, these views of the need for change were derived from the need to overcome the two common barriers to latecomers' transitions identified in the literature. In the transitional phase, latecomers are exposed to more direct competition against the forerunning innovators, and have to strictly comply with global institutions and regulations such as the IPR. In turn, they face increasing pressure to build innovative capability.

The existing studies on Asian NIEs examined the ways in which latecomers dealt with the common barriers found in fast-following contexts. Technological learning in most successfully caught-up industries was strengthened by reversing the PLC and under a highly vertical SIS, placing *Chaebol* in the highest position. They were mostly electronics and ICT hardware. These markets were stratified by price and quality, making it easier for latecomers to gradually penetrate them. The physical decomposability of the products to subcomponents also contributed to the stepwise technological and market catch-up, that is, modular product-based industries.

In contrast, this thesis captured the quite unfamiliar picture of the industrial characteristics surrounding the transition in the KoPI. First, the pharmaceutical industry operates in the dichotomised markets between off-patent generic drugs and patented original drugs. A significant science base is a necessary condition for entering the market for original drugs. In terms of technological learning, the industry has a long product development cycle from bench to market. Moreover, in the midst of the KoPI's transition, the burgeoning biotechnology paradigm expanded the science base associated with drug R&D.

Accordingly, public innovation actors and biotechnology-based start-ups increasingly undertake some of the central R&D roles in the pharmaceutical SIS. Meanwhile, no incumbent pharmaceutical firm has served as an 'anchor' firm, as *Chaebol* do in other

industries. The lack of large firms that can invest in start-ups' research outcomes and bear the risks of the extended R&D time frame can be problematic. Moreover, the nature of an integral product, combined with the difficulties posed by the physical decomposability of drugs into subcomponents, necessitates more in-depth and simultaneous interactions among the heterogeneous innovation actors. The division of R&D becomes particularly blurred for integral products.

While the thesis mapped the different dynamics of the transitional phase in the pharmaceutical industry, it highlighted the need for the radical reinforcement of the exploratory mode of technological learning to deal with the transition barriers. Thus, the key issue of the thesis is about the transformation of imitation-supportive institutional conditions and organisational processes to promote exploratory learning for developing new drugs. Few previous studies have dealt with the complex dynamics of a transition in a science-based industry with integral product architecture.

The following sub-sections summarise the transformational process in dealing with the institutional and organisational dynamics unveiled in the empirical work. There is an emphasis on the overall pattern of the transition, and the factors that influenced exploratory learning and transition rate are reported.

9.2.2 Institutional mechanisms of exploratory learning

The thesis addressed the influence of revised S&T policies on innovation actors' exploratory learning, which is the key mode of technological learning for new-drug development (*RQ 1*). Three major S&T policies to promote exploratory learning were considered: investment policy, an incentive regime and the administrative pattern of R&D support by relevant ministries. The findings suggest that the present status of the transition can be thought of as the synthetic outcome of both positive and negative influences of the policy factors on technological exploration.

Specifically, the investigation focused on capturing how each policy category promoted or interrupted the expression of the key characteristics of exploratory learning in each R&D organisation, such as risk taking and the long-term nature of learning (*RQ 1.1*). The investigation also traced whether the policies facilitated or disturbed interactive learning between the public and industrial innovation actors, which is the other key feature of exploration in the science-based pharmaceutical industry (*RQ 1.2*).

The investigation first showed that the active investment policy contributed to the establishment of exploration-capable public and private innovation actors. However, it

also revealed that the latecomers' 'real' exploratory learning was fairly inhibited in organisations; it was also not cross-fertilised between the public and industrial actors given the incentive regime and administrative pattern of R&D support. Moreover, the findings pointed out that the negative aspects of the policy factors partly stemmed from the fast followers' institutional legacy of risk-averse and short-term performance, together with institutional inexperience in promoting exploratory learning in integral product-based industries. The operational patterns of the policy factors identified in the discussion (Chapter 8) are summarised as follows:

Policy factors that promoted exploratory learning

- R&D investment led to the establishment of the necessary innovation actors for science-based innovation, such as universities, GRIs and biotechnology start-ups (*RQ 1.1*).
- R&D investment decreased the initial risk in conducting technological exploration, that is, new-drug R&D, for incumbent pharmaceutical firms (*RQ 1.1*).
- The incentive regime emphasising publication led to the rapid accumulation of a stock of scientific research, which can drive further exploratory learning (*RQ 1.1*).

Policy factors that interrupted exploratory learning

- R&D investment focusing on emerging biotechnology missed the importance of the incumbent pharmaceutical industry as the commercial channel for biotechnology research (*RQ 1.2*)
- The incentive regime overemphasised quantity-based performance, such as the number of publications, which led to a risk-averse tendency in public actors' exploratory learning (*RQ 1.1*).
- The incentive regime – specifically the publication-oriented evaluation of most innovation actors – disturbed joint exploratory learning between the public and industrial innovation actors (*RQ 1.2*).
- The incentive regime, led by the professor-dominated selection environment of NRDPs and their interest in upstream research, overlooked the commercial viability of exploratory learning (*RQ 1.2*).
- R&D support under compartmentalised ministries (MOST, MOHW and MOTIE) failed to coordinate their different goals for R&D support and caused the misalignment of upstream and downstream incentives for exploration (*RQ 1.2*).

- R&D support under the compartmentalised ministries disturbed the close exploratory learning links across diverse NRDPs, although such links are important for exploration in integral architecture-based drug R&D (*RQ 1.2*).

To sum up, the thesis showed that fast followers have limited institutional capability to promote exploratory learning. The negative effects of Korea's S&T policies led to a systemic inefficiency that counteracted the positive policy effect of enhancing exploratory learning. Specifically, the S&T policies inhibited risk-taking and long-term exploration practices in public R&D organisations and DBFs (*RQ 1.1*). Moreover, they also interrupted mutually compatible joint exploratory learning between the public and industrial actors (*RQ 1.2*). This means that upstream biotechnology research (led by the public actors) and pharmaceutical R&D (headed by industrial actors) were largely decoupled from each other.

9.2.3 Organisational mechanism of exploratory learning

The thesis also examined firm-level R&D processes for new-drug development. It aimed to gain an understanding of latecomer firms' enhancement of the exploratory mode of technological learning (*RQ 2*). An empirical analysis was conducted by examining the changes in the new-drug development process of nine latecomer firms between the completed first round of new-drug R&D and the on-going second round, in terms of both technological development (*RQ 2.1*) and organisational mechanisms (*RQ 2.2*). Findings suggest that the present status of the industrial transition is partly an outcome of the continuous error correction process of latecomers' awkward exploratory learning over the past 25 years.

Specifically, the findings showed that procedural, strategic and organisational learning factors were limited in effectively actualising the key characteristics of exploratory learning in new-drug R&D. The results further showed that this limitation was considerably due to the intermingling of the organisational effort for innovation and the on-going organisational memory of imitative learning. Taking these together, there is an overall commercial failure in the initial replication stage to follow first movers' exploration model, and recent rectifying efforts to improve the profitability of technological exploration. The most influential factors identified in the discussion (Chapter 8) are summarised as follows:

Factors influencing latecomer firms' exploratory learning

- The drug R&D practice was conducted with a low degree of interaction among R&D teams, and used the technology-push approach without profound market consideration (*RQ 2.1* and *2.2*).
- The time strategy of new-drug R&D, that is, the time-to-market of exploratory learning, was considered late after the commercial failure of the NCEs, which took 10 years (*RQ 2.1*).
- R&D paths have recently started to diversify into four niche fields – IMDs, QOL-oriented NCEs, phytomedicines and biological drugs – after the failure of the NCEs that solely focused on antibiotics and anticancer, which have a major market (*RQ 2.1*).
- The organisational structure of R&D showed a tardy change from a function-based to a product/project/matrix-based structure to promote interactive and market-reflective R&D (*RQ 2.2*).
- The arm's-length organisational structure of R&D showed the effectiveness of securing long-lasting exploration in small latecomer firms (*RQ 2.2*).
- Top management, often company owners, played a supportive role in maintaining long-running new-drug R&D within firms. However, the other concerned groups had a more negative view of company owners' roles in industry-wide innovation activities (*RQ 2.2*).
- A risk-averse and imitation-routinised mind-set still underlay the firms' exploratory learning to some extent (*RQ 2.1* and *2.2*).

On the whole, the findings show that latecomer firms were delayed in building a virtuous cycle of exploratory learning and profit creation because of certain procedural and strategic defects involved in the new-drug R&D process (*RQ 2.1*). The delay can be partly attributed to some problems in the organisational mechanism of conducting exploratory learning (*RQ 2.2*).

Particularly, the tough R&D process demonstrates that intense exploratory learning itself does not necessarily guarantee a successful transition for latecomers. This is particularly true if learning is not considered in the strategic and organisational context of direct competition against Big Pharma. The thesis further argues that complementary competition against Big Pharma can be an effective niche model for latecomers' exploratory learning.

9.3 Theoretical Contribution

This thesis makes four theoretical contributions, particularly in relation to the conceptual framework for understanding technological learning in the transitional phase: the catch-up dynamics of latecomers' science-based transition in an industry that operates integral product architecture (Sub-section 9.3.1), the system perspective of exploratory learning (Sub-section 9.3.2), the suggestion for a transformative capacity (Sub-section 9.3.3), and the non-technological factors that commercially vitalise technological learning (Sub-section 9.3.4). These four conceptual perspectives help build a comprehensive conceptual framework for the transitional phase of industrial development.

9.3.1 Science base, product nature and catch-up

The thesis fills a theoretical lacuna in the literature on both science-based innovation and latecomers' catch-up. Studies on science-based innovation have largely focused on advanced countries and their firms. They have generally emphasised the collaboration between public science and industrial actors. Behind this, the literature has tended to assume the prior accumulation of research capability in the innovation actors observed (Chapter 2, Section 2.5.3). However, this thesis addresses latecomers whose public and industrial actors only started to accumulate a science base in the past two decades. Thus, understanding the initiation mechanism of science-based innovation activities becomes as important of an issue as collaboration.

The literature on catch-up also overlooks the process of catch-up in a science-based industry, particularly in an integral architecture-based sector such as the pharmaceutical industry. Instead, the literature mainly focuses on modular, product-based industries, which were notably successful in a rapid catch-up led by *Chaebol* (Chapter 2, Section 2.5.3). However, as shown, the technological nature of integral products is very different, and these differences affect the organisational and institutional mechanisms of technological learning.

The thesis provided a deeper understanding of the dynamics of latecomers' technological learning and competition in a science-intensive and integral product-based industry that was fairly distinctive from the modular, product-based industries traditionally associated with catch-up (See Sub-section 9.2.1). Few studies have examined science-based catch-up by latecomers making integral products, at least in the context of Asian NIEs.

9.3.2 System perspective of exploratory learning

The conceptual framework combined a firm-level theory of organisational learning (focused on the distinction between exploration and exploitation) with literature on the innovation system. It attempted to identify the inter-organisational and systemic influence of exploratory learning. As seen, interdependence and interactivity among heterogeneous innovation actors and the influence of diverse policy elements undergird the exploratory learning of an individual innovation actor. Thus, the application of the concept of organisational learning to the systems level enabled the thesis to analyse institutional perspectives on the concept of exploratory learning. The existing literature on exploration and exploitation has mostly focused on firm-level ambidexterity and inter-firm perspectives on exploration in advanced countries. The systemic aspects of exploratory learning, such as institutional influence, were rarely addressed in the latecomer context.

9.3.3 Transformative capacity

The transformative view, associated with the idea of a pattern change, provided a complementary conceptual lens to conventional catch-up frameworks; this helped capture the procedural problems that latecomers encountered in the transitional phase. Knowledge is accumulated continuously by ascending the catch-up stages, but, as shown in this study, the transition to advanced development stages requires a discontinuous mode of organisational mechanisms and institutional settings from the previous imitation stage. The transformative view expounded in this thesis helps show that the underlying problems of the KoPI's technological learning stemmed from institutional and organisational discontinuity in the transitional phase.

This transformative view has rarely been employed in the literature analysing Asian NIEs' rapid catch-up at both firm and national levels. Some concepts widely adopted in the literature, such as absorptive capacity (e.g., Kim 1997b), combinative capability (Mathews and Cho 1999) and government-led, strong innovation systems (Kim 1998), tended to focus on the dynamics of the incremental improvement of technological learning. This seems to be an academic response to interpret the rapid catch-up of Asian NIEs and their firms. However, this thesis noted that such an incremental and continuous view of catch-up has limitations in interpreting the changing pattern of technological learning and its procedural difficulties in the transitional phase.

The transformative view did not extend to theorise the factors of transformation. However, by interpreting some factors that were discussed in the literature on science-based innovation and the catch-up, this thesis was able to trace the institutional and

organisational strengths and weaknesses in promoting the key characteristics of exploration in a science-based industry.

In this regard, idea of transformative capacity can be seen as a more comprehensive, dynamic capability for latecomers that embraces institutional and organisational factors. This concept seems to be particularly appropriate for understanding the system's and firm's momentum to advance to the next development stage.

9.3.4 Non-technological factors

The thesis extended the recent theoretical argument on the non-technological factors in latecomers' advanced catch-up (e.g., Dutrenit 2004, Hobday et al. 2004, Hobday 2005). By examining the strategic and organisational factors of the exploratory mode of technological learning, the thesis shed light on the reasons why latecomer pharmaceutical firms failed to reach a position of more value creation, despite achieving a moderate level of innovative technological capability.

One of the most noticeable non-technological factors discussed in the recent literature (Hobday et al. 2004, Hobday 2005) is the conceptualisation of alternative innovation paths for catch-up, aspired for by the Gerschenkronian view (1965). However, few empirical studies have been conducted on such conceptualisation, and little attention has been paid to the elements that can enable it to occur. This thesis empirically captured the practical effectiveness of latecomer firms devising their own catch-up paths. It further suggested a few strategic and organisational tactics that would enable firms to do so.[219]

9.4 Implications in Practice

A few practical lessons are suggested to policymakers and managers. These lessons are particularly concerned with the institutional and non-technological conditions that promote long-running, highly uncertain and interactive technological learning in the transitional phase.

9.4.1 Implications for S&T policies

[219] Although a few recent studies of successful cases of innovation stressed non-technological learning factors in latecomers' advanced catch-up (e.g., Dutrénit 2000, Kale 2005, Medeiros 2011), some of the key non-technological factors identified in these cases had to do with the institutional factors, rather than the firms' internal factors. These included the loose IPR regime (Kale 2005) and domestic market protection (Medeiros 2011). In contrast, the transition of the KoPI apparently added more weight to, first, the latecomers' strategic and organisational capability to deal with the growing institutional and technological complexity during their transitional phase, and, second, the ability to deal with the competition against first movers.

First, it seems to be necessary for the government to consider the differences between fostering technologically ill-defined science-based innovation and supporting engineering industries in which the development route of technologies is largely predictable. As discussed above, the distance between technological learning and the market in science-based innovation is far wider than that in engineering industries. This research pointed out the negative effects of the short-term performance oriented evaluation system of national R&D investment in pharmaceutical R&D. The evaluation policy should be reformed to accept more long-term and failure-tolerant R&D activities. For example, one possible solution is a change in evaluation interval from annually to every three to five years.

Second, the government's capability to align diverse industrial and non-industrial (social) policies should be reconsidered. Although the government increasingly supported biotechnology, led by MOST and MOTIE, its R&D investments were poorly linked with industrial R&D. Industrial R&D was mainly guided by the non-industrial public-health policy of the NHI. As a result, all innovation actors responded to their various incentives differently, with some focusing on publications and others on imitation-based generic drugs.

Another issue is the institutional mismatch between the integral architecture products of the pharmaceutical industry and the compartmentalised R&D support of concerned ministries. This caused institutional confusion in implementing S&T policies.

Overall, the government in the transitional phase should put more emphasis on policy alignment with sector-specific knowledge dynamics and with heterogeneous incentive mechanisms, as many industrial sectors now have multi-technological bases and a variety of social and environmental perspectives. Policy alignment seems to be the major challenge for the government, given the on-going ministerial tendency to control umbrella organisations and expand the juridical scope to relevant sectors.

9.4.2 Implications for innovation management

This thesis highlighted the complementarity of the latecomers' innovation path, which sought to fill gaps in the product and technology portfolio of Big Pharma. In doing so, latecomers can create niche business opportunities, bypassing direct competition against leading industrial players. This is a very useful strategy to tackle transitional barriers.

There are three practical lessons for those who would pursue such a strategy in the context of complementary competition. First, a commercially feasible alternative innovation path can be formulated by focusing R&D on product segments that have a low degree of exposure to direct competition against market dominators. At the same time, the time frame of exploratory learning to market should be jointly conceived with the selection of the focal R&D area. Second, modifying the organisational structure of R&D centres should be properly timed, in tune with the changing pattern of technological learning. However, organisational experiments seem to be inevitable in the absence of a universal solution to the relationship between technological learning and organisational structure. Third, in this context, the operation of a quasi-arm's-length R&D organisation would be an alternative way to maintain mid- and long-term exploratory learning.

9.5 Limitations and Possible Further Studies

The limitations of this study mainly concern the methodology. The first methodological limitation relates to the absence of a specific case study of NRDP that could integratively show the effect of S&T policy reform on firms' exploratory learning. Most NRDPs were fragmented, focusing only on certain R&D steps, and no NRDP conducted comprehensive upstream and downstream R&D stages. Thus, the policy influence on exploratory learning was probed by observing the operational pattern of several NRDPs in a general context. Ironically, this limitation of selecting proper and specific NRDPs may partly reflect the structural defects of the present S&T policies, which are led by compartmentalised ministerial leadership.

Second, reliance on qualitative data based on interviews might have misled the argument regarding the problematic policy implementation to indicate the complete failure of the joint exploratory learning, that is, the entire absence of R&D collaboration. Interview data may suffer from recall bias or other biases that mislead the researcher. The research was meant to reveal the underlying qualitative problems of the transitioning innovation system, which were generally concealed by the quantitative performance of national resource input, such as the rapid increase in publications, patents, and technological transfer. Such data, when considered out of context, can veil the innovative viability of technological learning in the transitional phase.

Third, as Bell (2006) pointed out, it is worth remembering the effect of the observation period in making a correct research argument. As the analysis showed, if the KoPI is considered after completing the second round of new drug R&D in the coming ten years, some might say that the sectoral transition has proceeded smoothly. For example, a few

new drug candidates are now in the process of NDA or the last stage of clinical trials in the US.[220] However, in 2013, this research uncovered institutional and organisational problems that the KoPI has clearly experienced for the last 25 years of new drug R&D. When other latecomers attempt to challenge the technological exploration, these institutional and organisational problems should not be neglected.

Therefore, the following issue is recommended for investigation in future research: the government reinforced the Pharmaceutical Industry Promotion Act to facilitate innovation-oriented R&D as the first industry-specific industrial policy in the last 15 years. In 2012, the government launched a large-scale multi-ministerial and public-private collaborative R&D programme to develop innovative drugs, the Korea Drug Development Fund, which now supports 23 projects. It also established a policy to support exports to the US market called the Columbus Project (The Korea Herald, 04/03/2011). Moreover, the drug pricing policy under the NHI system has begun to be linked with the rate of firms' R&D expenditure. That is, at the macro-level, the government at last seems to be attempting to emulate the industrial policy supporting the KoPI and to align relevant S&T policies.

Thus, KDDF projects could be analysed to determine the effect of institutional rearrangement on the enhancement of Korean pharmaceutical firms' exploratory learning. Such research would provide a deeper understanding of the science-based innovation and institutional and organisational problems in cultivating the key mode of technological learning for the latecomers' transition.

9.6 Final Remarks

The transitional dynamics explored in this thesis addressed how firms strengthen technological exploration for innovation at the micro-level, and how institutions reformulated exploratory learning-friendly innovation systems at the macro-level. These tasks involved unbundling the imitation focused learning routines and institutional frameworks. This research has highlighted the difficulties involved in this transformational process. In spite of increasing national resource input and the moderate success of technological catch-up, the transition has demanded sophisticated institutional and non-technological learning strategies for successful changes in patterns to highly uncertain, long running and interactive learning. As the thesis has shown, this

[220] E.g., NCEs: DA-7218 and Zydena by Dong-a; Biological drugs: IVIG (Intravenous immunoglobulin) by GC and SR-hGH (Sustained Release-human Growth Hormone) by LGLS; IMD: Esomezol by Hanmi as the first IMD of Nexium by AstraZeneca.

has not been easy. But important lessons have been learnt. We end on a quote that summarises this well:

> The development of new drugs differs greatly from that of generic drugs. New drug R&D can be compared to musical composition, in which an original work is created. The composition requires various steps and skills, such as theory, creativity, musical notation, orchestration, and repeated experimental performances. Before a performance, even the composer cannot confirm whether the work will properly be realised in the harmonisation of players and instruments. In contrast, the development of generic drugs can be regarded as the proficient performance of a well-known musical masterpiece. The players concentrate only on mastering the existing piece to achieve a good performance (Comments by Dr Seung-ju Lee, Director of Sanofi-Aventis).

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Appendix 1 A summary of the literature on the influence of biotechnology on the pharmaceutical industry

Title (Authors)	Theoretical framework	Implications
Complementarity and external linkage: The strategies of the large firms in biotechnology (Arora and Gambardella 1990)	• Firms' strategies for external linkage	• The correlation between large firms' four strategies of external linkage. • The strategies are complementary (agreements with other firms, research agreements with universities, investments in the capital stock of NBFs and acquisitions of NBFs). • Suggestion that the locus of innovation is considered as a 'network' of inter-organisational relations.
Does biotech reflect a new science-based innovation regime? (Coriat et al 2003)	• Technological regimes • Science-based industry • Institutional complementarities (e.g. university, patent, finance)	Distinction between two types of science-based regimes, stressing the role of basic sciences and thereby universities, patents and venture capital in Type 2. (Type 1 generally describes electronics & ICTs)
Pharmaceutical firms and the transition to biotechnology: A study in strategic innovation (Galambos and Sturchio 1998)	• The emergence of new technologies • Strategic alliances	• Pharmaceutical firms' changing strategies as biotechnology continues to develop. • Strategic alliances with start-ups in order to acquire specific biotechnology, followed by the establishment of in-house R&D capabilities in biotechnology. • Networking and collaboration

Title (Authors)	Theoretical framework	Implications
When does start-up innovation spur the gale of creative destruction? (Gans et al 2002)	• Innovation by start-ups • Inter-industrial differences	• Identifies firms' commercialisation strategies with respect to cooperation and competition. The probability of cooperation is highest in biotechnology where the relative costs of acquiring complementary assets are high and the environment offers a strong IPR regime. • The degree of IPR strength, and transaction and sunk costs for entering a product market determine a firm's commercialisation strategy. c.f. electronics.
Does good science lead to valuable knowledge? Biotechnology firms and the evolutionary logic of citation patterns (Gittelman and Kogut 2003)	• Scientific research and innovation performance • Epistemic community of scientists and firms' activities	• Shows a conflicting evolutionary logic between scientific research-generating knowledge and innovation activities due to firm's private use of scientific knowledge.
Social networks, learning, and flexibility: Sourcing scientific knowledge in new biotechnology firms (Liebeskind et al 1996)	• Social networks • Organisational learning and flexibility	• Supports the positive effect of boundary-spanning social networks to promote organisational learning and foster organisational flexibility in two identified biotechnology start-ups. This is difficult to achieve due to the market and/or self-contained hierarchy mechanisms.

Title (Authors)	Theoretical framework	Implications
Innovation and market structure in the dynamics of the pharmaceutical industry and biotechnology: towards a history-friendly model (Malerba and Orsenigo 2002)	• The evolution of the industry • Modelling the innovation activities in search, research and the market	• The penetration of biotechnology into the pharmaceutical industry does not represent a competence-destroying process. It shows the relationship between a lack of cumulativeness in innovation activities, market fragmentation (and concentration) and the emergence of a new technological paradigm (biotechnology), suggesting the necessity for collaboration between incumbents and start-ups.
Coherence of the knowledge base and firm innovative performance: Evidence from the US pharmaceutical industry (Nesta and Saviotti 2005)	• The economy of scope and scale • The dynamics of the knowledge base (coherence and scope) • Incumbents and DBFs	• The positive effects of the coherence of the knowledge base on firms' innovative performance. • Coherent firms are more successful than incoherent ones because they can enjoy the economies of knowledge scope by sharing similar scientific and technical competencies and common complementary assets.
Knowledge networks as channels and conduits: The effects of spillovers in the Boston biotechnology community (Owen-Simit and Powell 2004)	• Dynamics of the R&D network • Economic geography	• The central role of key nodes in a network as carriers of the rules and practices of inter-organisational R&D based on geographical propinquity and the institutional characteristics of the key members in the network. • The practices and commitment of network nodes can be identified through two types of network nodes: ○ A permeable channel is suitable for a set of organisations that emphasises open science in variable environments. ○ Closed conduits offer reliable and excludable information transfer at the cost of fixity in stable environments, and are more contractual.

Title (Authors)	Theoretical framework	Implications
Knowledge, integration, and the locus of learning: An empirical analysis of process development (Pisano 1994)	• Knowledge integration • Learning process	• The choice between learning by doing and learning before doing depends on the degree of accumulation of prior knowledge bases. • Traditional chemical-based drug production processes are relatively governed by learning before doing, while learning by doing is more important for biotechnology-based production. • These choices influence the lead times between process research and real production.
Interorganizational collaboration and the locus of innovation: Networks of learning in biotechnology (Powell et al 1996)	• R&D network • Learning process	• The locus of innovation is found within the inter-organisational networks that sustain a fluid and evolving community. Access to these networks is thus critical in order to explore and learn. Two processes of learning occur to enhance the inflow of specific information, resources and products. • The emergence of networks is due to the disparate sources of knowledge and the uncharted pathways of technological development in biotechnology.

Title (Authors)	Theoretical framework	Implications
Network dynamics and field evolution: The growth of interorganizational collaboration in the life sciences (Powell et al 2005)	• R&D networks and centrality • Institutional evolution	• The diversity of institutional forms – public, private and non-profit – that are active in the evolution of the organisational field of the life sciences arises from the different selection environments. These institutional features promote dense webs of connectivity that, once in place, influence both subsequent decisions and the trajectory of the field. • Shows how the topology of networks emerged and injected novelty into an institutional system. It argues that the evolution of the field is predominantly shaped not by money or market power but by organisations positioned in the centre with diverse portfolios of well-connected collaborators. This was tested by the introduction of four logics of attachment – accumulative advantage, homophily, follow-the-trend and multi-connectivity.
Organizational integration of acquired biotechnology companies in pharmaceutical companies: The need for a hybrid approach (Schweizer 2005)	• M&A research • Organisational integration and the capabilities of firms	• Stresses the importance of post-acquisition processes in integrating biotech know-how, technology (biotech knowledge) and capabilities. It argues in favour of an integration strategy to realise preservation, symbiotic acquisitions and absorption acquisitions at different paces across the diverse value chain components.
Commercializing knowledge: University science, knowledge capture, and firm performance in biotechnology (Zucker et al 2002)	• Commercialisation of universities • Science and firms' performance • The nature of knowledge and the role of scientists	• The involvement of star scientists in teamwork (production) between universities and firms is critical for successful innovation. It is attributed to the complexity and tacitness of knowledge.

Appendix 2 List of interviewees and background

	Interviewee	Position – Organisation (the former or present position)	Area	Date of the Interview
1	Dr. Han-seung Ko	Managing director of bio-health research – Samsung Advanced Institute of Technology (The present CEO of Samsung Bioepis)	Large firm (*Chaebol*)	20 August 2008 (Phone interview)
2	Dr. Eun-kyu Lee	Professor, Department of chemical engineering – Hanyang University	University	27 August 2008
3	Dr. Seung-yong Hwang	CEO – Genocheck; Professor, Department of biochemistry, Hanyang University	DBF	27 August 2008
4	Dr. Bong-hyun Chung	Director of bionano research centre – Korea Research Institute of Bioscience and Biotechnology (KRIBB)	GRI	28 August 2008
5	Beyong-wha Lee	CEO – Macrogen	DBF	28 August 2008
6	Dr. Jong-ho Lee	Director – Macrogen	DBF	28 August 2008
7	Jin Kong	Director of biochip department – Optrontech	DBF	29 August 2008
8	Dr. Su-kyung Kim	CEO – Nanostroage	DBF	1 September 2008
9	Dr. Han-oh Park	CEO – Bioneer	DBF	2 September 2008
10	Dr. Eui-sung Yun	Principal researcher of biomicro-system research – Korea Institute of Science and Technology (KIST)	GRI	3 September 2008
11	Dr. Ji-yoon Kang	Principal researcher of bionano research centre –KIST	GRI	3 September 2008
12	Dr. Won-yong Ko	Director – Panagene	DBF	4 September 2008
13	Dr. Mun-yeon Jeong	– Electro Telecommunication Research Institute	GRI	4 September 2008

14	Dr. Kookjin Lim	Manager of Diagnostic research – LG Life Sciences	Large firm (*Chaebol*)	5 September 2008
15	Dr. Je-kyun, Park	Professor, Department of Biosystem – Korea Advanced Institute of Science and Technology	University	8 September 2008
16	Pan-yun, Park	Researcher – Biomedlab	DBF	9 September 2008
17	Keum-yeong Lee	Team manager – Biomedlab	DBF	9 September 2008
18	Dr. Sung-hwan Ahn	CEO – GenomicTree	DBF	11 September 2008
19	Seok-kyun Jeong	Director of technology marketing – KMac	SME	11 September 2008
20	Dr. Mun-hee Han	CEO – Proteogen (the former president of Korea BioIndustry Organization and the former head of genetic research centre of KIST)	DBF	12 September 2008
21	Seul-ki Lee	General manager – Proteogen	DBF	12 September 2008
22	Dr. Hyung-il Jeong	Professor, Department of life science and biotechnology – Yonsei University	University	18 September 2008
23	Dr. Se-whan Park	Professor, Department of biotechnology and bioinformatics – Korea University	University	22 September 2008
24	Dr. Seok-kwan Kim	Research fellow – Science and Technology Policy Institute (STEPI)	GRI	25 September 2008
25	Dr. Eu-jin Han	Research fellow – Korea Institute of Intellectual Property (KIIP)	GRI	26 September 2008
26	Dr. Min-gon Kim	Principal researcher of bionanotechnology research – KRIBB	GRI	30 September 2008
27	Dr. Eun-seong Kim	Senior researcher of biotechnology policy centre –KRIBB	GRI	30 September 2008
28	Dr. Mu-ung Kim	Researcher of biotechnology policy centre –KRIBB	GRI	30 September 2008
29	Dr. Jin-seo Park	Researcher – Korea Institute of Science and Technology Information (KISTI)	GRI	2 October 2008
30	Seung-yeon Cho	Researcher, LIG Investment & Securities	Company	20 October 2008

31	Dr. Sung-wook Hong	Professor, College of life science – Seoul National University	University	23 October 2008
32	Dong-hun Hyun	Researcher, R&D planning and coordination team, Daeduk R&D Institute – Honam Petrochemical Co.	Large firm (*Chaebol*)	26 February 2009
33	Dr. Joong-myung Cho	CEO – Crystal Genomics (the former head of drug research centre of LG Life Sciences)	DBF	31 August 2010
34	M.D., PhD. Ku-chan Kim	Science Ambassador of MSD – Merck & co (the former head of the centre for the genome science, Korea National Institute of Health)	Big Pharma	8 September 2010
35	Se-jin Park	Chief Financial Officer (CFO) – LegoChem Biosciences (the former manager of LG Life Sciences)	DBF	10 September 2010
36	Dr. Yong-ju Kim	CEO – LegoChem Biosciences (the former head of drug research centre of LG Life Sciences)	DBF	10 September 2010
37	Nak-keun, Seong	Manager of the product development – LG Life Sciences	Large firm (*Chaebol*)	
38	Dr. Sung-ju Lee	Director of R&D in Korea, Sanofi-Aventis (the former researcher of LG Life Sciences)	Big Pharma	13 September 2010
39	Dr. Sung-ik Park	Manager of the product development – Green Cross	K-Pharma	14 September 2010
40	Dr. Eun-cheol Heo	CTO – Green Cross	K-Pharma	14 September 2010
41	Jong-ik Park	Head of the planning and coordination – Celltrion	DBF	15 September 2010
42	Heon-je Cho	Head of drug R&D policy – Korea Drug Research Association (KDRA)	Industrial association	28 September 2010
43	Jae-soon Kim	Head of global business development – Hanmi Pharmaceutical	K-Pharma	6 October 2010 (Phone interview)
44	Chang-ju Choi	Manager of information management, Central R&D institute – Hanmi Pharmaceutical	K-Pharma	7 October 2010
45	Dr. Maeng-sup Kim	CTO – Hanmi Pharmaceutical	K-Pharma	7 October 2010

46	Dr. Myung-ho Bae	Head of R&D strategic planning, Central R&D centre – Yuhan Corporation	K-Pharma	8 October 2010
47	Dr. Jae-gyu Kim	Director of new drug research, Central R&D centre – Yuhan Corporation	K-Pharma	8 October 2010
48	Dr. Soon-hoe Kim	CTO – Dong-a Pharmaceutical	K-Phama	8 October 2010
49	Dr. Byung-moon Kim	Managing director of Biotechnology R&D centre – Dong-a Pharmaceutical	K-Pharma	8 October 2010
50	Dr. Kyu-heum Na	Senior research scientist – Dong-a Pharmaceutical	K-Pharma	8 October 2010
51	Dr. Sung-gon Kim	Head of new drug research group, Central R&D centre – CKD	K-Pharma	
52	Dr. Sung-sook Lee	CTO – CKD	K-Pharma	
53	Yon-sam Oh	Chief Legal Officer (CLO) – HanAll BioPharma	K-Pharma	14 October 2010
54	4 e-mail interviews	Viromed (DBF), Ilyang (K-Pharma) and JW (K-Pharma) Korea Health Industry Development Institute (KHIDI)	DBF K-Pharma GRI	8 July 2010, 15 July 2010 14 June 2013
55	2 anonymous interviewees	Ministry of Science and Technology (MOST)	MOST	July 2011 – Aug 2011

Appendix 3 Interview questionnaire

1. The technological capabilities of Korean pharmaceutical companies

- The degree of innovation of the Korean pharmaceutical industry
  - Technological quality of the new drugs developed by local companies
  - Reasons for the commercial failure of new drugs
  - Levels of upstream research, translational research and clinical development
  - Reasons for the focus on incrementally modified drugs (IMDs) and phytomedicines
  - Commonalities and differences between the drug R&D and engineering industries and their influence on the emergence of the science-intensive pharmaceutical and biotechnology industries – organisational, cultural, business and institutional contexts

- Involvement in biotechnology R&D
  - Overall direction of R&D in the industry: new biological drugs vs. biosimilars
  - Potential of the stem cell business and reasons for the business rush in Korea
  - Entry of *Chaebol* into the biotechnology industry and the potential for its success
  - Relationship with synthetic drugs: complementary vs. competitive

2. Technological and organisational capabilities of own company

- The drug R&D strategy of the company
  - History of its R&D activities
  - Background and processes with respect to the R&D of its first new drugs
  - Reasons for the failure/success of its new drugs
  - Changes in its new drug R&D focus between the initial and present stages
  - Reasons for a focus on both generic and new drug R&D
  - Strengths and weaknesses of its R&D capabilities
  - Biotechnology strategy: new biological drugs, biosimilars, stem cell therapy
  - Strategy for global development and relationship with Big Pharma
  - Technological and commercial potential of phytomedicines

- Organisational and managerial issues
  - Organisational structure of R&D centre and its strengths and problems
  - Organisational differences in the development of generic drugs and new drugs
  - Organisational integration of biologists and chemists
  - Role of the owners in new drug R&D
  - Role of the experienced researchers recruited from Big Pharma
  - Organisational inertia: generic drug developers vs new drug researchers
  - Reasons for the stagnancy in M&A in the industry
  - Internal inhibitor/promoter to open innovation

3. Technological capabilities of and relationships with other types of innovation actors

- Perceived innovativeness and drug R&D strategy of other case firms
- Relationships with GRIs, universities and DBFs (conversely, their perspective of the pharmaceutical companies)
- Reasons for collaboration with public actors/DBFs
  - Positive and negative perspectives regarding the behavioural patterns of public actors and DBFs
  - Trust/distrust among the innovation actors (especially, between the pharmaceutical firms and DBFs)

4. Regulatory and market environments

- Influence of the reform of National Health Insurance on new drug R&D
- Regulatory and approval systems of KFDA
- Influence of other stakeholders such as medical doctors and chemists
- Problems with the venture capital system in its support of high-risk long-term drug R&D (compared to the ICT industry)
- Roles of the ministries and their support of biotechnology and NRDPs
  - Positive/negative role of MOST: S&T policies, its inclusiveness of industrial R&D
  - Positive/negative role of MOHW: public health policies and industrial R&D
  - Positive/negative role of MOTIE: New technology centred industrial policies

Appendix 4 Survey questionnaire for the interview

설문조사자: 황성웅(s.hwang@sussex.ac.uk)

Innovation Capability of Korean Bio-pharmaceutical Firms

Do you think the development of the biopharmaceutical industry has been successful until now in Korea?

☐successful ☐lagging ☐failure

Annual R&D expenditure: _____(KRW)

Bio and pharmaceutical related SCI papers and domestic patents:

N. of articles-_____, **N. of patents-**_____

N. of Researchers for biotechnology business

N. of PhD -_____	N. of MSc -_____	N. of BA -_____

1 Which R&D activities are the relatively strong and weak points of your company?

Strong	**weak**
☐ Basic, explorative and discovery research	☐
☐ Validation, application and translational research	☐
☐ Exploitation stages (development or preclinical test)	☐
☐ Clinical stage	☐
☐ Regulatory and approval stage	☐
☐ Reverse engineering	☐
☐ Others: _____	

2 Has your company participated in national R&D projects based on biotechnology?

☐ Yes ☐ No

If you have, what is the main reason for participating in the national R&D projects?
: _____

3 What types of R&D capability does your company want to acquire and learn when it collaborates with universities and GRIs?

☐ Discovery, exploration and basic research
☐ Application and translational research
☐ Core technologies ☐ Technology transfer only
☐ Peripheral or frontier technologies and knowledge
☐ Others: _____

4 Number of R&D collaborations or alliances for exploration and discovery: _____

What type of organization has been your main partner for collaborative research?

☐ hospitals ☐ universities ☐ pharmaceutical firms
☐ DBFs ☐ GRIs ☐ focusing on in-house development

(5 ~ 7) Questions	Difficult	Relatively difficult	Average	Relatively successful	Successful
Effectiveness of collaborative R&D with GRIs	☐	☐	☐	☐	☐
Effectiveness of collaborative R&D with universities	☐	☐	☐	☐	☐
Effectiveness of collaborative R&D with DBFs	☐	☐	☐	☐	☐

8 What is the main obstacle in collaborating with universities and GRIs?

☐ Lower potential to commercialize or for scale-up
☐ Different value estimation between universities/GRIs and private sectors
☐ Others: _____

9 What is the main obstacle in collaborating with DBFs

☐ Lower potential to commercialize or for scale-up
☐ Different value estimation between DBFs and pharmaceutical firms
☐ Others: _____

10 What is your firm's main strategy to make profits with your drug R&D projects?

☐ Sales of patents
☐ Technology transfer after pre-clinical trial
☐ Technology transfer after clinical stage 1
☐ Technology transfer after clinical stage 2
☐ Technology transfer after clinical stage 3
☐ Through own marketing channel
☐ Others: _____

11 If you have ever suspended or stopped R&D projects before their completion, what has been the main reason for this?

☐ Delay or failure in screening, discovery or exploration
☐ Delay or failure in validation, application or translation
☐ Delay or failure in pre-clinical or development stage
☐ Delay or failure in clinical test or the test of prototype
☐ Delay or failure in meeting approval and regulatory system
☐ Failure in collaboration with outside organizations
☐ Insufficiency of financing ☐ Lack of capability in marketing

12 What are the other institutional reasons of the laggard in commercialization of research and discoveries, and of the unilateral upstream research lacking the reflection of downstream or market issues?

(13 ~ 15) Questions	Not at all	Not much	Average	Important	Very important
How much has the government's R&D programme influenced the direction of R&D projects?	☐	☐	☐	☐	☐
How important is the benchmarking or imitation of existing products in R&D activities?	☐	☐	☐	☐	☐
How much has the government's policy of fostering biotechnology sectors influenced the direction of R&D projects?	☐	☐	☐	☐	☐

16 Have you ever experienced any organizational or technological resistance when your company moves from the existing main R&D activities to the emerging biotechnology R&D? _____

17. Question	Difficult	Relatively difficult	Avera -ge	Relatively successful	successful
Do you think that your company's R&D strategy and direction have adapted well to the health and welfare policies?	☐	☐	☐	☐	☐

18 If the development of Korea's biotechnology industry is lagging in commercializing or making profit, what are the reasons for this?

☐ Mismatch between the health and welfare policies, and the industrial policy
☐ Regulation and approval system
☐ Ineffectiveness of the industrial policies to foster
☐ Mismatch between the pharmaceutical-related policies and the biotechnology-policies
☐ Lack of medical centres for clinical testing
☐ IPR regime
☐ Others: _____

Appendix 5 Comments about the evaluation system based on PBS

Interviewee	Comments
Interview 7 (DBF)	Researchers in DBFs have tended to consider their R&D projects not as market products but as research performances.
Interview 9 (DBF)	In Korean DBFs, the first business model is to acquire NRDPs. To do so, the publication performance must be good.
Interview 12 (DBF)	The government focuses on where the R&D funds are spent (i.e., auditing). They do not concentrate on research performance because they lack the ability to evaluate scientific research.
Interview 19 (SME)	In the past, there was little to gain in collaboration with universities through NRDPs. Although the recent quantitative accumulation of scientific publications is remarkable, creative and industrial-potential research performance should be emphasised. In the public sector, displaying research performance through publications is critical in securing R&D projects, whereas private firms give priority to the industrial value of research for profit.
Interview 22 (University)	In most NRDPs, strictly speaking, there is no clear demarcation between science and technology projects. One of the reasons is the criteria used in performance evaluation. NRDPs weigh the impact factor of publications as the value of the innovative application of the projects. In this situation, it would be very difficult to generate industrially meaningful innovation.
	Researchers in GRIs and universities have no choice but to follow the criteria of evaluation. If the performance were evaluated in terms of its quality, they would have to follow the norm. If the performance were considered based on the quantity of publications, they would have to meet this criterion.
Interview 26 (GRI)	The research in GRIs generally takes both directions of R&D – industrial R&D, which can directly contribute to the firms' technological development, and the implementation of fundamental R&D. In reality, however, the yearly publication based evaluation system inhibits both types of R&D activities.
Interview 31 (University)	In Korean universities, there has been a strong tendency to focus on studies published by a small number of scholars and to publish follow-up articles on these studies. Even so, there are few problems in maintaining academic fame and acquiring new projects.
Interview 33 (DBF)	The total amount of national R&D funding for biotechnology is by no means small. The problem is that the allocation of funds has become excessively fragmented. The funds have been transmuted to budgets for publishing research in universities. Meanwhile, GRIs have directly engaged in new drug development. How can inexperienced researchers really develop [marketable] new drugs? After all, NRDPs turned to sharing funds across the various stakeholders in biotechnology R&D.
Interview 36 (DBF)	The success rate of NRDPs is over 80%. Why? Because NRDPs do not allow failure. Hence, researchers are supposed to ensure the success of

	their projects. However, nothing really has been produced. Short "termism" persists. Why can't a project continue for 10 years?
Interview 38 (Big Pharma)	Although new drug R&D needs to start by identifying the market demand by medical doctors, because of the evaluation system GRIs and universities have tended to concentrate on research topics that are easily published and patented. These topics are generally far from the demands of the clinical market.
Interview 39 (K-Pharma)	In academia, professors have tended to concentrate on the latest research topics, which get the attention of policy more easily, thus acquiring NRDPs. In contrast, in private companies, the technological realisation and commercial potentiality of the newest research topics are difficult to predict.

Appendix 6 Comments about the selection problems of NRDPs

Interviewee	Comments
Interview 2 (University)	It cannot be denied that there has been a tendency by committee members to prefer their own academic or research subjects when they select projects for the NRDPs.
Interview 7 (DBF)	National R&D projects are concentrated on a small number of DBFs, which are based on academic networks and the reputations of CEOs.
Interview 9 (DBF)	In NRDPs, even NRDPs in industrial development, academia is too influential, although recently the industrial voice seems to have gradually gained attention. Once the direction of NRDPs is suggested by a small number of specialists, most researchers have tended to follow the research trend, much like ‘flying geese’.
Interview 14 (*Chaebol*)	The professors are too powerful in planning S&T policies, so these policies are less reflective of the industrial situation. Under the *Chaebol* led catch-up stage through imitation, it was not a big problem for industry. The demand level of university research was low from the industry at that time. However, in order to cope with the pressure to innovate, industry has increasingly demanded higher levels of university research and direct support by NRDPs of industrial R&D.
Interview 34 (Big Pharma)	Biotechnology research itself is of the utmost importance. However, in terms of the global R&D trend in new-drug development, of 7,500 clinical trials, only about 400 are of biological drugs. That is, the main market is still in synthetic drugs, although biologics have potential in the future. In the case of the UK, there is the MRC, which controls the big picture and macro level strategies. We don't have such an organisation. Although the national science and technology commission is under the President, government-sponsored professors are in charge. They routinely seek to make policy plans for their own interests such as upstream research.

Interview 36 (DBF)	The total number of NRDPs is almost 8,000, which is too fragmented. Many similar projects are given in different names among public R&D actors. For effective new drug R&D, NRDPs need to be more selective and have a longer focus.

Appendix 7 Patent trend broken by R&D fields in the case firms

Dong-A

R&D fields		1960s	1970s	by 1987	1988-1999	2000- 2010
NCEs					13	22
Phytomedicine					4	5
IMDs (DDS, composition, structure)					9	26
Process development		3	10	21	26	7
Biotechnology	Product				5	8
	Method				15	2
Total number of patents		3	10	21	72	70

Green Cross (GC)

R&D fields		1960s	1970s	by 1987	1988-1999	2000- 2010
NCEs					3	10
Phytomedicine					2	3
IMDs						
Process development				4	1	3
Biotechnology	Product			1	90	47
	Method			5	67	30
Total number of patents				10	163	93

*

Yuhan

R&D fields		1960s	1970s	by 1987	1988-1999	2000- 2010
NCEs				1	15	22
Phytomedicine						
IMDs (DDS, composition, structure)					13	15
Process development		1	1	12	20	20
Biotechnology	Product				2	13
	Method				10	10
Total number of patents		1	1	13	60	80

Hanmi

R&D fields		1960s	1970s	by 1987	1988-1999	2000- 2010
NCEs					1	16
Phytomedicine						
IMDs (DDS, composition, structure)					18	59
Process development					7	37
Biotechnology	Product				2	10
	Method				2	11
Total number of patents					30	133

LG Life Sciences (LGLS)

R&D fields		1960s	1970s	by 1987	1988-1999	2000- 2010
NCEs					35	38
Phytomedicine					2	3
IMDs (DDS, composition, structure)					3	20
Process development					18	20
Biotechnology	Product				22	16
	Method				28	31
Total number of patents					108	128

ChongKeunDang (CKD)

R&D fields		1960s	1970s	by 1987	1988-1999	2000- 2010
NCEs					10	13
Phytomedicine						1
IMDs (DDS, composition, structure)					10	20
Process development			2	11	18	24
Biotechnology	Product				5	6
	Method			2	9	5
Total number of patents			2	13	52 (35%)	69 (35%)

JoongWae (JW)

R&D fields		1960s	1970s	by 1987	1988-1999	2000- 2010
NCEs					17	10
Phytomedicine						
IMDs (DDS, composition, structure)					12	12
Process development			3	16	25	6
Biotechnology	Product					5
	Method				2	1
Total number of patents			3	16	56 (46%)	34 (18%)

Dongwha

R&D fields		1960s	1970s	by 1987	1988-1999	2000- 2010
NCEs					27	13
Phytomedicine						4
IMDs (DDS, composition, structure)					4	10
Process development			1	9	8	7
Biotechnology	Product				3	1
	Method				3	
Total number of patents			1	9	45 (18%)	35 (20%)

Ilyang

Technological fields		1960s	1970s	by 1987	1988-1999	2000- 2010
NCEs					8	2
Phytomedicine					2	
IMDs (DDS, composition, structure)					13	12
Process development			4	7	14	8
Biotechnology	Product				6	1
	Method				4	2
Total number of patents			4	7	47 (30%)	25 (32%)

Appendix 8 Case firms' increase in publication and those of subject areas[221]

Companies	By 1987	1988-1999	2000-2005	2006-2011	Total
Dong-A	7 (5)	21 (21)	44 (31)	54 (39)	126 (49)
GC (Green Cross)[222]	2 (3)	117 (44)	134 (50)	191 (53)	444 (73)
Yuhan	5 (5)	35 (20)	15 (17)	38 (32)	93 (41)
LGLS	-	117 (38)	78 (35)	138 (40)	218 (51)
Hanmi	-	6 (3)	6 (7)	44 (25)	56 (28)
CKD	-	9 (2)	12 (7)	16 (16)	37 (17)
JW	-	26 (18)	24 (13)	32 (20)	82 (31)
Dongwha	-	24 (27)	37 (28)	9 (13)	70 (43)
Ilyang	-	7 (11)	7 (8)	-	14 (17)
Total number of publication	14	362	357	522	1,140

Appendix 9 Change in the R&D personnel of case firms

Companies	2014	2005 (No. of PhDs)	1998
Dong-a	227	194 (18)	90 (9)
Green Cross	448	161 (31)	-
Yuhan	315	227 (23)	131 (12)
Hanmi	434	150 (11)	-
CKD	405	64 (11)	-
JW	171	144 (25)	-
LG Life Sciences	300	328 (62)	-
Dongwha	102	73 (8)	66
Ilyang	95	68 (5)	61

Source: Data from the Financial Supervisory Service (http://dart.fss.or.kr), Kim (2006), Medipharma news (11/12/2014), and interviews.

[221] Although the publication data (based on a search of ISI Web of Knowledge data) is not directly related to the main analysis, it clearly shows the deepening and widening scientific knowledge base of the case firms over the last 20 years' transitional phase as primary evidence of the transition towards SBFs.

[222] The number includes the publication by its independent research institute, MGRI. GC only published 245. Also, the number of JW includes publications by its joint research institute of C&C Research Laboratories. JW only counted 45. In the case of LGLS, it was established as an independent company in 2003. There seem to be some omissions in counting the number published between 2000-2005, due to its name change (at maximum about 62). Dongwha and Ilyang have struggled with the shrinking market performance over the last ten years, while they have kept their active drug R&D.